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CUTANEOUS CARBOHYDRATES

I. THE NORMAL SKIN

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The metabolism of carbohydrates in normal and in pathologic skin has been studied by a number of investigators without revealing its general pattern. A few isolated facts related to this problem have been ascertained, but relatively few of definite and unquestioned significance. There is disagreement about even some of the fundamentals. The solution of the problem has been difficult in many respects because of the lack of reliable quantitative methods of analysis for small portions of skin. Relatively recent developments have improved this situation. Consequently it seems propitious to again make a careful analysis and survey of the dextrose and glycogen content of normal skin, so that comparisons with pathologic skin may be more significant.

A rather wide range of values has been quoted for the normal dextrose content of human skin. Only those of rather recent publication are considered here, since the older methods of determining such values are not considered reliable. Urbach and Sicher [1] in 1929 and Urbach and Rejtö [2] in 1932 found the normal value for dextrose to be 47 mg. per hundred grams of skin, and in 1937 with a refined method, Urbach, Depisch and Sicher [3] reported 61 mg. Trimble and Carey [4] in 1932

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1. Urbach, E., and Sicher, G.: Beiträge zu einer physiologischen und pathologischen Chemie der Haut: III. Der Zuckergehalt der Haut unter physiologischen und pathologischen Bedingungen, Arch. f. Dermat. u. Syph. **157**:160, 1929.

2. Urbach, E., and Rejtö, K.: Beiträge zu einer physiologischen und pathologischen Chemie der Haut: XI. Ueber den freien und "gebundenen" Zucker in der Haut unter physiologischen, experimentell veränderten und pathologischen Bedingungen bei Mensch und Tier; ein Beitrag zum Kohlehydratstoffwechsel der Haut, Arch. f. Dermat. u. Syph. **166**:478, 1932.

3. Urbach, E.; Depisch, F., and Sicher, G.: Zum Problem des isolierten hohen Hautzuckers bzw. Hautdiabetes, Klin. Wchnschr. **16**:452, 1937.

4. Trimble, H., and Carey, B. W., Jr.: On the True Sugar Content of Skin and of Muscle in Diabetic and Non-Diabetic Persons, J. Biol. Chem. **90**:655, 1931.

studied what they called the true sugar value of normal human skin, finding 56 mg. The figures for animal skin vary considerably with different species but are fairly constant for any particular species. For dogs various authors [5] report from 60 to 101 mg., for rabbits from 105 to 155 mg., for mice from 53 to 81 mg. and for rats from 80 to 104 mg.

Few reliable reports on the glycogen content of human or animal skin are to be found in the literature. Fahrig [6] found about 71 mg. per hundred grams of what he calls the inner true skin and 157 mg. for the same amount of outer skin of human beings. Pillsbury and Sternberg [7] determined the glycogen content of the skin and liver of dogs on various diets and found in the skin about 108 mg. with a low carbohydrate diet, 137 mg. with a high carbohydrate diet and 75 mg. with a high fat, low carbohydrate diet. Variations in the liver were much greater than those in the skin. Narahara [5b] found glycogen in the skin of rabbits ranging from 5 to 67 mg., with an average of 34 mg. Gualdi and Baldino [8] and Yuyama [9] microscopically detected in the sweat glands considerable glycogen, eliminated largely during functional activity. Matsumoto [5c] found in normal rabbit skin a glycogen content of 86 mg. The figures for glycogen are variable and indicate that the methods may be not entirely satisfactory or at least not standardized.

The areas from which the samples of skin are taken must be considered. Fahrig [6] found 0.2269 mg. of glycogen per hundred grams of human epidermis from the mammary region, and 0.3442 mg. in that from the leg. Matsumoto [5c] found that the sugar content of the skin

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5. (*a*) Pillsbury, D. M., and Kulchar, G. V.: The Use of the Hagedorn-Jensen Method in the Determination of Skin Glucose, J. Biol. Chem. **106**:351, 1934. Urbach and Sicher.[1] Trimble and Carey.[4] (*b*) Narahara, K.: Experimentelle Untersuchung über den Hautzucker: IX. Hautglykogen und Zuckerabbau in der Haut, Jap. J. Dermat. & Urol. (Abstr. Sect.) **35**:31, 1934; abstracted, Biol. Abstr. **9**:1727, 1935. (*c*) Matsumoto, Y.: An Experimental Study of the Carbohydrates of the Skin, with Special Reference to the Combined Sugar (Protein Sugar) and the Glycogen: I, Mitt. a. d. med. Akad. zu Kioto **7**:1307, 1933. (*d*) Matsumoto, Y.: II, ibid. **8**:481, 1933. (*e*) Moncorps, C.; Bohnstedt, R. M., and Schmid, R.: Ueber den Zucker- und Glutationgehalt von Blut und Haut bei Hohsonnen- und Crotonoldermatitis, ein Beitrag zur Frage periperisch bedingter Stoffwechselvorgänge, Arch. f. Dermat. u. Syph. **169**:67, 1934.

6. Fahrig, C.: Ueber den Kohlehydratumsatz der Geschwülste und ihrer normalen Vergleichsgewebe sowie seine Beziehungen zum Milchsäurehaushalt des Körpers, Ztschr. f. Krebsforsch. **25**:146, 1927.

7. Pillsbury, D. M., and Sternberg, T. H.: Relation of Diet to Cutaneous Infection, Arch. Dermat. & Syph. **35**:893 (May) 1937.

8. Gualdi, A., and Baldino, N.: Ricerche sul metabolismo per variazioni della temperatura locale dei tessuti; il contenuto in glicogeno e in acido lattico della cute e dei muscoli raffreddati, Riv. di pat. sper. **5**:318, 1930.

9. Yuyama, H.: Ueber die histologische Untersuchung der Glykogenverteilung in der leprösen Haut, mit besonderer Berücksichtigung der Beziehung zwischen der Funktion der Schweissdrüsen und der Schwankung des Glykogens, Jap. J. Dermat. & Urol. (Abstr. Sect.) **37**:134, 1935.

of the back was lower than that of other parts, while the glycogen content was highest in the skin of the back, less in that of the flank and least in that of the abdomen and extremities. Fahrig found decided differences in the glycogen content of the outer and inner parts of the skin, as mentioned in the foregoing paragraph. On account of these wide variations in observations among different authors one concludes

TABLE 1.—*Summary of Prior Reports on Dextrose Content of Skin*

Date	Authors	Dextrose, Mg./100 Gm.			
		Man	Dog	Rabbit	Mouse
1927	Folin, Trimble and Newman	..	67 (fasting)		
1929	Urbach and Sicher	47	60	117	53
1931	Trimble and Carey	56	..	...	..
1932	Urbach and Rejtö	47	84	134	58
1933	Matsumoto	..	..	112	..
1933	Matsumoto	..	91	114	..
1934	Narahara	..	..	115	..
1934	Pillsbury and Kulchar	..	..	105	..
1934	Moncorps, Bohnstedt and Schmid	..	..	...	81.3
1937	Urbach, Depisch and Sicher	61	101	155	69

TABLE 2.—*Summary of Prior Reports on Glycogen Content of Skin*

Date	Authors	Glycogen, Mg./100 Gm.		
		Man	Dog	Rabbit
1903	Schondorff, quoted by Rothman	724 (Av.) (92.7 to 1,680)	..	..
1927	Fahrig	157 (outer true skin) 71 (inner true skin)		..
1927	Folin, Trimble and Newman, quoted by Rothman	..	17 (fasting)	
1930	Gualdi and Baldine	..	70	..
1933	Matsumoto	..	188 (tail)	86 82 (6)
1933	Matsumoto	..	..	87 (16)
1934	Narahara	..	..	34 (Av.) (5 to 67)
1937	Pillsbury and Sternberg	..	108 (low carbohydrate diet) 137 (high carbohydrate diet) 75 (high protein diet)	
	Tabulae biologicae, vol. 3	61	26 (fasting)	

that the method of taking samples, the areas from which samples are taken, the preparation of the skin for analysis and the methods of determining dextrose and glycogen must be standardized before one may expect to have agreement in results. However, most investigations are based on comparative changes so that variations among different authors may not be significant enough to warrant dispute, provided each investigator determines his control value carefully.

The ratio of cutaneous sugar to blood sugar, according to Urbach, Depisch and Sicher,[3] varies with different species but is constant for

each particular species. They reported a ratio of 61 : 103 (skin sugar : blood sugar) for human beings, 69 : 108 for mice, 101 : 96 for dogs, 104 : 83 for rats, 147 : 111 for guinea pigs and 155 : 108 for rabbits. Narahara [5b] reported a ratio of 115 : 104 for rabbits. Matsumoto [5c] reported 112 mg. of sugar per hundred grams of normal rabbit skin. Sellei and Spiera [10] observed a ratio of 139 : 108 in fasting rats and 180 : 174 when the rats were on a mixed diet. They used figures for total reducing substances, which they found to be 20 to 30 per cent higher than the actual sugar values. This again shows the necessity for standardization of procedures.

Various authors have investigated what has been called bound sugar, those reducing substances which remain in the protein precipitate, perhaps glycoproteins, and are released on acid hydrolysis. Urbach and Rejtö [2] observed a greater percentage of bound sugar in the skin than in the blood and attached importance to the retention of it in the skin longer than in the blood after the feeding of dextrose. There are many possible reducing substances in various tissues which this method might separate and which would have no bearing on the normal metabolism of carbohydrates. Matsumoto [5c,d] has determined values for combined sugar (protein sugar) in an attempt to correlate it with the skin metabolism. Rabbits normally had 194 mg. of protein sugar per hundred grams of skin. This increased considerably after injection of dextrose. Up to the present it would seem that the importance of these bound sugars has not had wide acceptance. Intermediary carbohydrate metabolism may involve the interaction of various combinations of reducing substances, but it seems evident from numerous investigations that dextrose and glycogen are the most important indicators of normal or disturbed carbohydrate metabolism.

No doubt diet plays a prominent role in determining the amount of sugar and glycogen in the skin. On carbohydrate-poor diets, according to Urbach and Sicher,[1] the cutaneous sugar was 12 per cent lower (61 mg.) than on a carbohydrate-rich diet (73 mg.), while the amount of sugar in the blood remained practically at the same level with both diets. As previously mentioned, Pillsbury and Sternberg [7] found a higher glycogen content (157 mg.) in dogs fed a high carbohydrate diet than in those with a high fat and low carbohydrate diet (75 mg.). Rothman [11] stated that since with overfeeding the glycogen content of the cells of the skin, as well as that of the liver and muscle, was greater than that of the blood, it appeared that these cells built glycogen from lower carbohydrates. In all experimental work one can see the need of

10. Sellei, C., and Spiera, M.: Die Role der Haut im Kohlenhydratstoffwechsel, Biochem. Ztschr. **296**:83, 1938.

11. Rothman, S.: Kohlenhydrate der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, vol. 1, pt. 2, p. 268.

carefully controlling the diet, especially when attempting to establish normal values for carbohydrates of the skin.

With the administration of dextrose orally, the cutaneous sugar values parallel the blood sugar curve with a lag.[3] The cutaneous sugar reaches its peak in about one hour and returns to normal in about three hours, as compared with one-half and two hours, respectively, for the blood. The changes in cutaneous sugar thus appeared to be due to a simple diffusion process. In pathologic skin the normal diffusion processes might be disturbed, so that such a relation between blood and cutaneous sugars would not be entirely comparable. In patients with diabetes and in depancreatized dogs Urbach observed that the cutaneous sugar rose much more decidedly and was maintained for a much longer period than was the blood sugar. Narahara [5b] found only slight variations in the cutaneous glycogen in the rabbit after feeding of dextrose, in spite of decided changes in cutaneous and blood sugar. Matsumoto [5c] injected dextrose in the ear vein of the rabbit and found parallel changes in the sugar content of skin and blood over a period of two hours, while the glycogen content remained practically unchanged with doses up to 1 cc. of a 40 per cent solution of dextrose. Two cubic centimeters of 40 per cent dextrose raised the cutaneous glycogen from 83 mg. to 133 mg. per hundred grams of skin in one hour (back to 74 mg. in two hours), while the cutaneous sugar was raised from 123 mg. to 251 mg. Ordinarily the increase in cutaneous glycogen may be a rather slow process, and considerable time may therefore be required to determine changes. Sellei and Spiera [10] determined the total reduction power of the skin and blood in rats and found parallel curves after subcutaneous injection of dextrose, substantiating the belief in a simple diffusion process for the change in cutaneous sugar. Cori [12] found that 17 per cent of the orally given dextrose absorbed in rats was converted into hepatic glycogen in three to four hours. About 45 to 50 per cent was oxidized (metabolism experiments).[13] About 36 per cent of the administered dextrose was found in the form of glycogen in the remainder of the body, which Cori assumed to be chiefly in the muscle. Determinations of cutaneous glycogen were not made, although a considerable part of the body glycogen might have been found there. The hepatic glycogen had reached its peak in about four hours and declined during the fifth hour in spite of continued absorption of sugar from the intestine. "Thus the par-

12. Cori, C. F.: The Fate of Sugar in the Animal Body: III. The Rate of Glycogen Formation in the Liver of Normal and Insulinized Rats During the Absorption of Glucose, Fructose and Galactose, J. Biol. Chem. **70**:577, 1926.

13. Cori, C. F., and Cori, G. T.: The Fate of Sugar in the Animal Body: II. The Relation Between Sugar Oxidation and Glycogen Formation in Normal and Insulinized Rats During the Absorption of Glucose, J. Biol. Chem. **70**:557, 1926.

ticipation of the liver in the disposal of sugar is negligible in the later periods of absorption." The skin may then play a more prominent role in the formation of glycogen. Cori suggested, however, that the muscle was probably the most important organ in glycogen storage. Folin, Trimble and Newman [14] gave dextrose intravenously to dogs and found the glycogen in the muscle only slightly higher thirty minutes after injection. From guinea pigs they were able to recover practically all the injected dextrose as free sugar in thirty minutes, analyzing the whole animal. There was, however, unequal uptake of sugar in various tissues analyzed individually. Practically no glycogen was stored during

TABLE 3.—*Effect of Intravenous Injection of Dextrose on Glycogen Content of Skin of Dogs*

	Glycogen, Mg./100 Gm.	
Experiment	Before Injection	Thirty Minutes After Injection
1	1,085	1,147
2	1,042	1,108

TABLE 4.—*Effect of Injection of Dextrose on Dextrose Contents of Blood, Skin and Muscle in Dogs.*

	Dextrose Thirty Minutes After Injection, Mg./100 Gm.		
Experiment	Blood	Skin	Muscle
1	412	390	154
2	360	276	89
3	286	322	141
Average for fasting dogs	84	67	54

that time. The cutaneous sugar closely followed the blood sugar, while the muscle sugar was much lower. They stated:

> One important outlet for sugar as it leaves the blood is the skin. The skin, however, is not a storage place for glucose or glycogen, for in the fasting condition (? hours) it contains practically no glycogen and only a trifle more sugar than the muscle.

If the dogs fasted only twenty-four hours, it is difficult to understand the failure of Folin and his co-workers to find glycogen in the skin. It would be reasonable to expect that prolonged fasting would deplete supplies of glycogen in all parts of the body. This would not indicate a lack of ability on the part of the skin to store glycogen any more than it would on that of the liver. Determinations of glycogen several hours after the feeding of dextrose would be needed to refute

14. Folin, O.; Trimble, H. C., and Newman, L. H.: The Distribution and Recovery of Glucose Injected into Animals, J. Biol. Chem. **75**:263, 1927.

or substantiate such an opinion. Cori [15] found that absorption of dextrose by the stomach takes place at a constant rate over several hours. Nevertheless, the blood sugar soon reaches its maximum in spite of the continued absorption, showing that the tissues after a short latent period take care of the dextrose as rapidly as it is absorbed from the intestine. Since tissue sugars also reach their peak in an hour or so, the further absorbed dextrose must be either burned or stored as glycogen. Folin and his associates [14] state

> As a temporary receptacle in response to sugar injections, the skin seems to us to be of much greater importance than heretofore appreciated. So far as concerns the influx of sugar into the skin, we have a number of experiments which seem to indicate clearly that the influx is the result of passive diffusion rather than of any special absorption or metabolic process.

Urbach, Depisch and Sicher,[3] on the contrary, saw in the elaborate intermediate carbohydrate metabolism in the skin, as well as in the variations in the cutaneous sugar level and tolerance curve, sufficient reason to deny emphatically any mere diffusion phenomenon.

The intrinsic metabolism of carbohydrates in the skin is still poorly understood. Various factors have been investigated in an attempt to throw more light on this problem. Pillsbury [16] studied the lactic acid content of rabbit skin and found about twice as much in the skin of well fed animals as in that of starved ones. In incubated skin he determined a normal curve for lactic acid production and found an increase when dextrose solution was added and still more when the solution was buffered with phosphate. Skin from rabbits given 3 Gm. of dextrose intravenously one-half hour previously produced about twice as much lactic acid as did controls. There must therefore be enzymes present in the skin that make possible the transformation of dextrose with production of lactic acid. Fahrig [6] presented evidence to support these findings. Moncorps, Bohnstedt and Schmid [5e] studied the sugar and glutathione contents of the skin of white mice and found that inflammation produced by irradiation caused changes in the amount of cutaneous sugar but practically none in that of glutathione. Nakamura [17] investigated acetaldehyde formation in incubated skin. He found small amounts in fresh human and guinea pig skin, whereas cadaver skin (twenty-four hours) was entirely without it. The addi-

15. Cori, C. F.: The Fate of Sugar in the Animal Body: I. The Rate of Absorption of Hexoses and Pentoses from the Intestinal Tract, J. Biol. Chem. **66**: 691, 1925.

16. Pillsbury, D. M.: The Intrinsic Carbohydrate Metabolism of the Skin: Preliminary Report of Experimental Studies, J. A. M. A. **96**:426 (Feb. 7) 1931.

17. Nakamura, Y.: Die Fermente der Haut: IV. Ueber den Zuckerabbau in der Haut, Biochem. Ztschr. **173**:258, 1926.

tion of dextrose or glycogen increased the production of aldehyde in normal skin. Sellei and Spiera [10] blocked the reticulo-endothelial system of the rabbits with injections of water blue and a gold salt, aurolin, and found that while this caused the blood sugar to remain stationary or to decrease, the cutaneous sugar rose. They concluded that the reticuloendothelial system has some function in carbohydrate metabolism.

The question of the storage of carbohydrate in the skin is important, since the skin comprises about 16 per cent of the entire body tissues by weight or three times that of the liver. Urbach and Rejtö [2] found that after dextrose was fed, the skin retained sugar much longer than did the blood, especially in depancreatized dogs, and concluded that the skin was an important temporary storage organ for sugar. Since high cutaneous sugar is possibly a factor in the severity of certain diseases of the skin, an antidiabetic regimen would be indicated in such conditions, especially if a dextrose tolerance test showed the cutaneous sugar to be abnormally high. Carrie and Koenig [18] have shown that patients with high blood sugar excrete abnormally large amounts of sugar onto the skin surface and are more prone to cutaneous diseases, therefore requiring more frequent bathing as a prophylactic treatment. The presence of large amounts of sugar in the skin when blood sugar is high merely supports the theory that a simple diffusion process maintains cutaneous sugar levels and does not indicate storage. In rabbits Narahara [5b] found that after ingestion or intravenous injection of dextrose the level of the cutaneous glycogen changed relatively little in spite of decided changes in the levels of blood sugar and cutaneous sugar. He therefore concluded that the skin was an important temporary receptacle for sugar but that it played little part as a storage organ for intermediary carbohydrate metabolism.

The importance of insulin in general body carbohydrate metabolism is well known and may be of considerable importance in the intrinsic carbohydrate metabolism and general health of the skin. Nakamura [17] in his investigation of the acetaldehyde formation in the skin observed that when insulin was added to a mixture of skin and dextrose and incubated, there was an increased production of aldehyde with cadaver skin but little change with normal skin. The probable reason for this is that normal skin already has an optimal amount of insulin present to carry on normal metabolism, while insulin is lacking in the cadaver skin. Insulin normally present in the tissues thus appears to play a significant role in cutaneous carbohydrate metabolism. Urbach and Sicher [1] have noted that insulin in amounts sufficient to produce con-

18. Carrie, C., and Koenig, R.: Ueber den Zuckergehalt auf der Haut bei Normalen und Diabetikern, Arch. f. Dermat. u. Syph. **173**:611, 1936.

vulsions in dogs caused a greater fall in blood sugar (90 mg. to 43 mg. per hundred cubic centimeters) than in cutaneous sugar (50 mg. to 30 mg. per hundred grams). In rabbits a blood sugar of 132 mg. fell to 25 mg., while a cutaneous sugar of 142 mg. fell to 53 mg. They pointed out a normal parallelism between blood and cutaneous sugar curves, but storage and retention of sugar in the skin took place in some cases. Leyton [19] expressed the belief that local insulin packs are beneficial in some cases of obstinate septic lesions of the skin through a stimulation of local carbohydrate metabolism. Sellei and Spiera [10] found that after insulin was injected subcutaneously in rats there was a decrease in the cutaneous reducing substances from a normal of 139 mg. to 120 mg. with 4 units of insulin and an increase of reducing substances to 158 mg. with 30 units. The blood reducing substances at the same time fell respectively to 45 mg. and 55 mg. from a normal level of 108 mg. They interpreted their results as indicating that after the injection of large amounts of insulin the skin endeavors for a certain time to act as a storage organ for carbohydrate. Cori and Cori [13] found that rats receiving injections of insulin and being given dextrose by mouth absorbed the same amount of sugar as the controls without insulin but deposited less glycogen and oxidized more dextrose. They expressed the belief that since a large percentage of the carbohydrate metabolism took place in the muscle, a condition developed with excess insulin whereby the muscle utilized larger amounts of dextrose and therefore left less for the liver to convert into glycogen. If the figures of various authors are comparable, one finds that with insulin the sugar of the skin was reduced, but not as much as that of the blood.[1] The total reducing substance was lessened with small amounts of insulin and increased with large doses.[10] This might indicate that up to an optimal amount insulin increases the metabolism of sugar in the skin but to a much less extent than that in the muscle. Therefore the cutaneous sugar is reduced and at the same time glycogen is deposited in the skin at an accelerated rate when there is excess of insulin. This tends to retain carbohydrate in the skin as a reserve supply.

Epinephrine is a normal circulating hormone which also has influence on carbohydrate metabolism, possibly of importance to the skin itself. Matsumoto [5d] injected it into rabbits, with the results shown in table 5. After the administration of the drug the cutaneous sugar rose as a consequence of the rise in blood sugar, whereas the glycogen decreases. This indicates that epinephrine given systemically mobilizes sugar, derived in part perhaps from the cutaneous glycogen. It is

19. Leyton, N.: Insulin in the Local Treatment of Persistent Septic Cutaneous Conditions, Brit. M. J. **1**:70, 1938.

impossible to decide in this experiment whether the increase in cutaneous sugar is due only to simple diffusion from the blood or partly to conversion of some of the cutaneous glycogen present.

The presence of many diverse local substances may influence cutaneous carbohydrate metabolism. Many physiologic experiments and clinical experiences have shown that histamine in the skin will dilate the capillaries and increase their permeability. It would therefore be logical to assume that abnormally large amounts of histamine produced locally or applied locally might affect the carbohydrate content of the skin by allowing more rapid diffusion of sugar from the blood stream into the skin than demanded by local metabolism, resulting in an abnormally high level of cutaneous sugar. On the contrary, epinephrine applied locally decreases the circulation of blood in the area. This may result in decreasing the diffusion of dextrose into the skin and thus lead to a disturbance in carbohydrate metabolism.

TABLE 5.—*Effect of Injection of Epinephrine on Sugar and Glycogen Contents of Skin of Rabbits*

	Sugar, Mg./100 Gm.	Glycogen, Mg./100 Gm.
Before injection	107	127
2 hours after injection	221	108
5 hours after injection	94	104

The application of heat locally is known to be beneficial in many cutaneous conditions, probably because it improves local circulation and aids the normal metabolism of the tissue. Ultraviolet irradiation and exposure to the sun's rays have been shown [5e] to have a tendency to be followed, if mild, by a fall in blood sugar on the third or fourth day of from 22 to 25 mg. per hundred cubic centimeters and, if productive of a rather severe erythema, by a rise of 18 to 25 mg. In white mice after ninety minutes' irradiation of the skin the cutaneous dextrose rose from a normal of 81 mg. per hundred grams of skin to as high as 165 mg. within eight hours. Cutaneous glutathione also rose from 76.1 mg. to 155 mg. Inflammation induced by application of croton oil caused the dextrose tolerance curve of the skin to rise much higher than that of normal skin. The changes produced were possibly due to local variations in diffusion of histamine, epinephrine or dextrose. Meyer [20] showed that certain doses of ultraviolet radiation increased the ferment action in the skin of rabbits as judged by an increased production of purpurogallin. Doses up to 2 Finsen units increased the production from 0.16 to 0.172; 2.5 units decreased it to 0.135, and

20. Meyer, H.: Alte und neue experimentelle Untersuchungen zur Wirkung des Lichtes, Strahlentherapie **23**:369, 1926.

still higher doses brought ferment activity to an end. All ferments which have to do with carbohydrate metabolism in the skin are very likely influenced by ultraviolet rays.

The beneficial action of roentgen rays in clearing up some cutaneous lesions may also be partly due to changes in the metabolism of the cutaneous cells. David [21] found that in general roentgen rays caused a dilatation of the cutaneous capillaries, probably through action on the Rouget cells. This may be the result of the formation of metabolites in the skin which in turn affect the Rouget cells. It is known that irradiation alters the oxidation and reduction reactions in tissues, and changes in the carbohydrate metabolism would therefore be expected.

With certain skin lesions the therapeutic use of various reducing substances leads to the recovery of normal tissue. Whether these effects are due to the action of such substances on abnormal factors present in the skin or to an improvement of the altered metabolism is not well known. However, since carbohydrate metabolism depends on various chemical transformations, reducing substances may have an important influence in this respect.

METHODS ADOPTED FOR DETERMINING THE AMOUNTS OF DEXTROSE AND GLYCOGEN IN THE SKIN

Dextrose.—Samples of blood were drawn from fasting patients and at the same time portions of skin [22] were taken from the back near the lumbar region. Ordinary biopsy punches, 9 mm. in diameter, were used to remove a piece of skin weighing about 50 mg. This was finely minced and weighed and then transferred to a test tube containing 5 per cent zinc sulfate. The test tube was heated on a water bath for six minutes, and then 1 cc. of tenth-normal sodium hydroxide and 0.5 Gm. of a specially prepared fullers' earth (Lloyd's reagent) were added. The test tube was shaken for two minutes and the material filtered. The filter paper was washed three times successively with 2 cc. of water. The dextrose in the filtrate was determined by the Hagedorn-Jensen method.

Glycogen.—The skin sample removed weighed from 50 to 100 mg. This was placed in a 15 cc. centrifuge tube to which was added 0.5 cc. of a 30 per cent solution of potassium hydroxide. This was heated on a water bath until a clear solution was obtanied, then 2 cc. of 95 per cent alcohol was added, and the material was mixed and centrifuged. The supernatant fluid was discarded. The precipitate was washed twice with 2 cc. of alcohol and was centrifuged after each washing. One cubic centimeter of 5 per cent sulfuric acid was added to the final washed precipitate. The material was heated on a water bath for one hour, cooled and neutralized with normal sodium hydroxide. The amount of dextrose in the neutralized solution was determined by the Hagedorn-Jensen method. From this the amount of glycogen was calculated.

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21. David, O.: Untersuchungen über den Einfluss von Röntgenstrahlen auf Kapillaren, Strahlentherapie **23**:366, 1926.

22. Dr. H. C. Schorr helped to obtain biopsy material.

23. Footnote deleted.

TABLE 6.—*Range of Values for Dextrose in Fifty-Six Subjects and Glycogen in Thirty-Three Subjects*

Dextrose		Glycogen
Skin, Mg./100 Gm.	Blood, Mg./100 Cc.	Skin, Mg./100 Gm.
60.2 to 81.5*	78.9 to 104.0*	68.1 to 84.7

* Three subjects were found with higher values. One proved to be diabetic, and the others could not be followed. The results of the tests on these subjects are not included here.

TABLE 7.—*Relation of Quantity of Cutaneous Dextrose and Glycogen to Layer of Skin* in Twenty Persons (Average Values)*

	Superficial Skin, Mg./100 Gm.	Deep Layer, Mg./100 Gm.	Blood, Mg./100 Cc.
Dextrose	80.5	62.1	88.3
Glycogen	75.0	46.9	

* A biopsy specimen was taken down to the subcutaneous layer and then divided equally horizontally.

TABLE 8.—*Dextrose Contents of Skin and Blood of Animals (Average Values)*

Animal	Skin, Mg./100 Gm.	Blood, Mg./100 Cc.
Cat	77.8	99.5
Dog	71.3	92.4
Guinea pig	104.7	148.2
Rat	77.2	127.6
Rabbit	96.9	160.3

TABLE 9—*Effect of Intravenous Injection of Dextrose on Conetnt of Dextrose in Skin and Blood, and of Glycogen in Skin, of Six Dogs (Average Determinations)*

	Dextrose		Glycogen in Skin, Mg./100 Gm.
	Blood, Mg./100 Cc.	Skin, Mg./100 Gm.	
Control	102.2	71.7	79.6
After injection of dextrose, 4 Gm. per Kg.			
½ hour	268.2	90.7	79.8
1 hour	212.7	127.2	80.9
1½ hours	180.7	155.8	81.7
2 hours	120.2	102.7	83.6
2½ hours	100.6	80.2	84.1

TABLE 10.—*Effect of Injection of Insulin on Contents of Dextrose in Blood and Skin, and of Glycogen in Skin, of Five Dogs (Average Determinations)*

	Dextrose		Glycogen in Skin, Mg./100 Gm.
	Blood, Mg./100 Cc.	Skin, Mg./100 Gm.	
Control	101.6	74.3	76.0
After injection of insulin, 50 units intravenously and 50 units subcutaneously			
½ hour	87.6	66.8	76.6
1 hour	61.1	60.4	82.1
1½ hours	35.9	46.0	86.6
2 hours	32.9	39.5	93.1

TABLE 11.—*Effect of Subcutaneous Injection of Epinephrine on Content of Dextrose in Blood and Skin, and of Glycogen in Skin, of Five Dogs (Average Determinations)*

	Dextrose		Glycogen in Skin, Mg./100 Gm.
	Blood, Mg./100 Cc.	Skin, Mg./100 Gm.	
Control	88.3	66.4	75.6
After injection of 0.05 cc. of solution of ephinephrine			
½ hour	99.7	80.1	77.6
1 hour	113.8	93.0	81.2
1¼ hours	124.3	104.8	82.9
2 hours	145.6	120.9	86.9
3 hours	163.7	150.2	93.8

TABLE 12.—*Effect of Intracutaneous Injection of Epinephrine and Histamine on Content of Dextrose and Glycogen in Skin of Three Dogs (Average Determinations)*

	Before Injection		Ten Minutes After Intracutaneous Injection of Stated Solution	
	Dextrose, Mg./100 Gm.	Glycogen, Mg./100 Gm.	Dextrose, Mg./100 Gm.	Glycogen, Mg./100 Gm.
Area 1 (control)	73.7	71.8	(1 cc. saline solution)	
			72.1	71.6
Area 2	75.8	74.6	(1 cc. 1:5,000 epinephrine in saline solution)	
			60.7	72.1
Area 3	76.7	75.2	(1 cc. 1:5,000 histamine hydrochloride in saline solution)	
			82.9	73.7

TABLE 13.—*Influence of Elimination of Hepatic Circulation* on Content of Dextrose in Blood and Skin, and of Glycogen in Skin, of Three Dogs (Average Determinations)*

	Dextrose		Glycogen in Skin, Mg./100 Gm.
	Blood, Mg./100 Cc.	Skin, Mg./100 Gm.	
Control	106.2	71.8	77.6
After elimination of hepatic circulation			
1 hour	90.2	68.3	76.1
2 hours	80.7	59.8	73.2
3 hours	73.0	50.7	68.1
4 hours	60.0	41.4	66.2

* The splenic vein was connected to the inferior vena cava by means of a glass cannula through which had been threaded a piece of internal jugular vein. The portal vein and the hepatic artery were tied off.

TABLE 14.—*Effect of Local Heat on Content of Dextrose in Blood and Skin, and of Glycogen in Skin, of Three Dogs (Average Determinations)*

	Dextrose		Glycogen in Skin, Mg./100 Gm.
	Blood, Mg./100 Cc.	Skin, Mg./100 Gm.	
Control	112.7	78.2	80.1
After heating with stand lamp on one area			
½ hour	.....	85.6	80.1
1 hour	.....	90.2	82.6
Infra-red lamp on another area			
½ hour	.....	92.1	81.6
1 hour	.....	100.6	82.9

TABLE 15.—*Influence of Phlorhizin on Content of Dextrose in Blood and Skin, and of Glycogen in Skin, of Three Dogs (Average Determinations)*

	Dextrose		Glycogen in Skin, Mg./100 Gm.
	Blood, Mg./100 Cc.	Skin, Mg./100 Gm.	
Control	112.6	71.7	77.6
After phlorhizin was given by mouth, 1 Gm. daily			
24 hours	82.1	50.2	75.3
48 hours	65.3	37.6	74.3

TABLE 16.—*Effect of Application of Ice to the Skin on Blood Content of Dextrose and Cutaneous Content of Dextrose and Glycogen in Three Dogs (Average Determinations)*

	Dextrose		Glycogen in Skin, Mg./100 Gm.
	Blood, Mg./100 Cc.	Skin, Mg./100 Gm.	
Control	102.8	74.6	69.7
After ice was applied to skin and left there throughout length of experiment			
10 minutes	.....	60.7	68.7
½ hour	.....	70.2	69.7
1 hour	.....	80.7	69.9
1½ hours	.....	82.7	70.1

TABLE 17.—*Influence of Unfiltered Roentgen Rays on Content of Dextrose in Skin of Two Dogs (Average Determinations)*

	Dextrose, Mg./100 Gm.
Control	88.6
After application of 350 roentgens	
24 hours	85.8
48 hours	87.3
96 hours	89.5
1 week	90.3

TABLE 18.—*Effect of Exposure to Ultraviolet Rays from Cold Quartz Mercury Vapor Lamp on Content of Dextrose in Blood and Skin, and of Glycogen in Skin, of Three Dogs (Average Determinations)*

	Blood	Skin			
	Dextrose, Mg./100 Cc.	Area 1 Dextrose, Mg./100 Gm.	(Right) Glycogen, Mg./100 Gm.	Area 2 Dextrose, Mg./100 Gm.	(Left) Glycogen, Mg./100 Gm.
Control	106.2	76.2	69.7	78.7	70.8
After irradiation for ten minutes with lamp 5 cm. from skin					
Immediately	....	75.1	69.8	77.6	70.4
20 minutes	....	80.1	69.6	78.9	69.7
40 minutes	....	90.1	70.1	78.7	70.2

RESULTS OF EXPERIMENTS

The intracutaneous injection of histamine caused the local cutaneous dextrose to rise and at the same time caused dilatation of the adjacent blood vessels. Contrariwise, the intracutaneous injection of epinephrine caused a decrease in the local dextrose and contraction of the blood vessels at the site. One explanation of this phenomenon is to assume a certain level of dextrose in the skin. This is an equilibrium point between the rate at which the skin disposes of dextrose and that at which it receives a supply. One factor governing the latter is the quantity of blood flowing past the skin site. If the blood vessels increase their size, as with the injection of histamine, and the skin's utilization of dextrose remains constant, then an accumulation of dextrose results. If the blood supply is reduced, as it is with the presence of epinephrine, then the dextrose at the site should fall if it is used up at a constant rate.

TABLE 19.—*Effect of a Reducing Agent (Chrysarobin)* on Content of Dextrose and Glycogen in Skin of Three Dogs (Average Determinations)*

	Right Side		Left Side	
	Dextrose, Mg./ 100 Gm.	Glycogen, Mg./ 100 Gm.	Dextrose, Mg./ 100 Gm.	Glycogen, Mg./ 100 Gm.
Control	80.2	72.1	79.6	74.6
After application of 10 per cent chrysarobin ointment to right side				
10 minutes	86.7	71.8	80.1	73.6
30 minutes	93.7	74.2	80.2	75.6
Control: Skin excised from both sides and then chrysarobin ointment applied to right side	76.2	....	79.9	....

* The chrysarobin was removed with ether and alcohol before the determinations of cutaneous dextrose were made.

This reasoning may explain the results obtained with the use of heat, cold, ultraviolet rays and reducing agents. Heat causes dilatation of the blood vessels and should cause a rise in cutaneous dextrose. Cold causes a contraction of the cutaneous vessels, followed later by dilatation. The dextrose first shows a fall followed by a rise. Ultraviolet radiation causes dilatation of the blood vessels, and in these experiments it raised the level of cutaneous sugar. It is probable that 10 per cent crysarobin is sufficiently irritating to increase the blood coming to the site of application. Chrysarobin increases the dextrose. Whether such agents as ultraviolet rays, reducing agents, cold and heat have a specific action otherwise in relation to dextrose can be shown only by further work. Do they alter the rate of the consumption of dextrose in the skin? These experiments do not answer this or related questions. They simply point to quantitative results without explaining the mechanism of their achievement.

An attempt was made to follow the suggestion of Urbach and determine the amount of what he calls bound sugar, but the results were so variable that they could not be trusted. In such an analysis the skin is subjected to the action of strong acid in an attempt to separate the sugar from complex materials, presumably mostly proteins. It is impossible to know just what materials are obtained from such a violent reaction as that of strong acid on tissues. Undoubtedly reducing materials are yielded that are not carbohydrates. Urbach has not shown that they are indeed the latter. I feel that to reckon all these reducing materials as dextrose is an error. The source of some of them may be glycoprotein.

The determination of the contents of dextrose and glycogen in the skin when the latter is subjected to various kinds of agents and modalities helps one to gain an insight into the carbohydrate metabolism of the skin. It is impossible with the present data to get a nearly complete picture of the carbohydrate metabolism of the skin. Urbach claimed that this tissue has a peculiar carbohydrate metabolism of its own. He denied that the dextrose present in the skin is a mere diffusion product from the blood. He cited his observations that the amount of dextrose in the skin of some animals, such as the cat, was much higher than in the blood. I could not duplicate his results with animals. In all my experiments on various animals, I found that the skin contained slightly less dextrose than the blood or in some cases about the same amount. It is my belief that the dextrose present in the skin is a diffusion product from the blood. It seems quite evident from the present data that the skin is not a site for dextrose storage. The cutaneous sugar rises and falls with the blood dextrose after a very short latent period.

After the transfer of quantities of dextrose into the skin from the blood, an increase occurs in the cutaneous glycogen. An appreciable period elapses, however, during this conversion of dextrose to glycogen. The skin can hold the flood tides of dextrose from receding rapidly only if it converts it to starch. When the recession occurs, the glycogen slowly ebbs too, to a certain degree. The levels of glycogen and dextrose do not necessarily follow each other. Under the action of insulin the dextrose of the blood and that of the skin decrease, while the glycogen of the skin shows an increase. It is known that one of the actions of insulin is to aid in the synthesis of glycogen.

Phlorhizin poisoning causes a decrease in the dextrose of the blood and skin but no change in the cutaneous glycogen, as shown in the present work. The present belief is that phlorhizin interferes with the reabsorption of dextrose by the renal tubules. This results in a steady loss of dextrose through the urine, which is shown in the end

by changes in the blood and by the fact that the level of the cutaneous glycogen does not follow the lowering level of the cutaneous dextrose. Evidently the levels of the two substances can be independent of each other. It seems to be shown here, too, that cutaneous glycogen does not exist merely to furnish locally needed dextrose.

Just what the purpose or action of cutaneous glycogen is one cannot say at present. Apparently, it does not exist in the skin merely as storage material to furnish dextrose, as does the glycogen in the liver. If the liver is removed the blood sugar drops rapidly. The store of glycogen in the muscles and skin is considerable and could maintain the level of the blood dextrose for an appreciable time were it available for that purpose. If an animal is starved and the glycogen of the liver is depleted, it is found that the store of muscle glycogen decreases little. This points toward muscle glycogen having an action of its own apart from that of furnishing dextrose. It appears that the metabolism of glycogen in the skin follows somewhat the form it takes in the muscle and not that in the liver. Just how far the glycogen is utilized as a material independent of that of dextrose will be seen after further study. An aid in this direction will come from the oxygen and carbon dioxide analyses in respiration experiments on pieces of skin. It is my intention to conduct such studies.

The possibility should be considered that glycogen exists as a protecting substance. One of the modern beliefs is that glycogen is necessary for the protection of detoxifying processes in the liver. These processes may really be concerned with the mechanism of immunity. The skin is supposedly concerned with immunity, and it may be necessary to have glycogen present for this purpose.

These studies show that the more superficial layers of the skin contain more carbohydrate than the deeper ones. This fact is probably accounted for by the difference in the number of cells present in the respective layers. It would seem that the quantity of carbohydrate present depends on the number of cells present.

SUMMARY AND CONCLUSIONS

The literature on the carbohydrate metabolism of the skin is reviewed and discussed.

The dextrose content of the normal skin (excluding the subcutaneous fat layer) ranges from 60.2 to 81.5 mg. per hundred grams.

The values for glycogen range from 68.1 to 84.7 mg.

There is a difference in the dextrose values found for the skin of different animals, but the amount in the skin is always related to the amount in the blood of the particular animal. The values for the blood are always greater than those for the skin.

The superficial layers of human skin contain more dextrose and glycogen than the deeper ones.

The intravenous injection of dextrose causes sharp rises in the dextrose content of the skin but very minor ones in the glycogen content. The dextrose curve for the skin parallels that for the blood, with a lag in its rise and fall.

The injection of epinephrine for its systemic action increases the content of dextrose and of glycogen in the skin. The changes in the dextrose value are greater and more rapid.

The injection of insulin for its systemic effect decreases the dextrose content of the skin and increases the glycogen. The directional change of the values for dextrose and glycogen can be opposite.

If the circulation to and from the liver is effectively stopped, the dextrose in the skin decreases in time, while the glycogen is reduced relatively little.

Phlorhizin poisoning lowers the levels of blood and cutaneous dextrose but does not always affect the level of cutaneous glycogen. This again shows that the levels of cutaneous dextrose and glycogen can be independent of each other. Cutaneous glycogen does not exist merely to furnish locally needed dextrose.

The intracutaneous injection of epinephrine reduces the quantity of dextrose at that site and at the same time produces minor decreases in the glycogen content.

The intracutaneous injection of histamine increases the dextrose content at that site and changes the glycogen value very little.

The effect of the contact of ice with the skin is first to reduce the dextrose content of that part of the skin. Later, when the skin becomes congested, the dextrose content is increased. At the same time the glycogen value remains stationary.

Local heat to the skin increases the quantity of dextrose at that site with little change in the glycogen content.

Ultraviolet radiation without heat (cold quartz mercury vapor lamp) increases the dextrose in the irradiated skin without affecting that of the nonirradiated parts. The glycogen content is not changed.

Three hundred and fifty roentgens of unfiltered roentgen rays does not influence the dextrose content of the skin during the period of a week following such irradiation.

A reducing agent (chrysarobin) increases the dextrose of the skin on which it is applied but does not change the glycogen content during the period of half an hour.

The present work does not corroborate the concept of bound sugar. The foundations for this concept appear to need reexamination.

The dextrose content of the skin is dependent on that of the blood; dextrose is freely diffusible in the skin as well as in other tissues and organs.

The pattern for the use of glycogen in the skin seems to be similar to that in the muscle but not to that in the liver.

Dextrose is not stored in the skin. Large additions of dextrose in the skin may be temporarily stored by conversion to glycogen. More work is necessary to discover the extent to which carbohydrate metabolism in the skin parallels that in the muscle. The indications of the present data are that it is somewhat similar in both.

ABSTRACT OF DISCUSSION

DR. G. V. KULCHAR, San Francisco: I cannot agree entirely with Dr. Cornbleet's interpretation of the data. Like most data, his are subject to more than one interpretation. There seemed to me to be several possible sources of error which I could not see rectified in his experiments. One is the use of anesthesia when the specimen is taken. Certainly his work shows that the local injection of vasoconstrictors and also the presence of vasodilators will alter the dextrose values. If he used no local anesthetic, I still would think that there was a possibility of the effect of emotional factors. Struggling by the animal will produce a considerable change in the dextrose content of the blood and also in that of the skin.

Another possible source of error which was not dealt with clearly in his report is the necessity of freezing the tissue immediately after removal. Certainly if the tissue is not immediately frozen there is the possibility of glycolysis and the conversion of sugar to glycogen.

It seems logical to explain all the results he obtained, particularly with the use of irritants, such as chrysarobin, ultraviolet rays, heat and cold, the last two of which have in the end the same vasodilator action, as locally injected vasodilators.

I cannot agree with him that the skin does not have an intrinsic carbohydrate metabolism of its own. Without going into too much detail, one of the things that leads me to this thought is that Dr. Cornbleet maintains that the sugar simply pours into the skin and back again by a simple diffusion process. Several things lead me to believe that this may not be the case. One is that if it were a simple diffusion process, one would expect the dextrose curves of the blood and skin to parallel each other after the injection of a large amount of dextrose. As a matter of fact, they don't; there is a considerable lag. The second thing which leads me to believe that this may not be the case is the demonstration of the formation of lactic acid in the skin by Pillsbury. He has merely, as he said, scratched the surface of this problem. It seems to me that intimately bound up with these questions, and particularly when infections of the skin are concerned, is the relation of the increase in cutaneous dextrose to changes in the water content of the skin. Alderson and I have shown that there is an increase in water in the skin following an injection of a large amount of dextrose and that the effect of large amounts of dextrose on pyogenic processes, particularly in the skin, is due not to deposit of dextrose in the skin but rather to an increase in the water content of the skin.

DR. M. B. SULZBERGER, New York: I am not competent to discuss this subject. However, Dr. Sharlit, who should have opened this discussion, was unable to come. He asked me to say a few words presenting his views on Dr. Cornbleet's contribution.

An even approximately correct understanding of the metabolism of the skin involves laborious and repeated efforts to establish the truth concerning the fundamental chemical units essentially implicated in that metabolism: hence the inevitably repetitious reports on dextrose and glycogen in the skin of human beings and animals. I consider Dr. Cornbleet's contribution especially important because his findings are based on more adequate sampling than most of the work reported in this field. Furthermore, I believe that he has supplied the most competent evidence yet available in substantiation of the contention that the dextrose concentration in the skin varies chiefly because of simple diffusion. He has, with the same laboratory technic of analysis and by several approaches, established the fact that an increase in the size of the capillary bed in the skin (hyperemia) consistently tends to increase the concentration of dextrose. And by the same token, his failure to influence materially the glycogen content of the skin under conditions of hyperemia corroborates the belief that diffusion alters dextrose concentrations.

Using the same technic, Dr. Cornbleet has observed that when any factor increases the local circulation of blood in a particular area, the dextrose in the skin of that area is also increased. This observation is not, I believe, subject to Dr. Kulchar's criticism of the possibility of error in technic.

Whether or not dextrose and glycogen can be said to be stored in the skin is chiefly a matter of definition of the concept "store." Surely the concentration of dextrose in the skin tends to follow that in the blood, and when rapid depletion of the dextrose in the blood is accompanied by a slower loss from the skin, one might look on this lag as evidence of "storage." Definitely, glycogen is not stored in the skin in the same way as in the liver.

Dr. Cornbleet's suggestion that the time has arrived to correlate what is known about the carbohydrates in the skin with the respiratory quotient of the skin is so true that it may be said to be obvious.

DR. THEODORE CORNBLEET, Chicago: I am sorry Dr. Sharlit's illness prevented him from being here.

The influence of anesthesia on the cutaneous sugar was studied. There is a slight difference with and without anesthesia, whether it is general or local. However, the conclusions from these experiments are not altered by this, inasmuch as all the values reported were found with the use of anesthesia, and the changes are all in the same direction. The comparisons and correlations are therefore valid. The conclusions drawn were controlled by results obtained without anesthesia.

The emotion evoked by taking the biopsy specimen does not materially alter the values of the cutaneous sugar. Even when considerable dextrose is injected directly into the blood stream, with enormous rise in the blood dextrose, there ensues an appreciable period during which no change occurs in the cutaneous sugar. Any change in the level of blood sugar caused by emotion is far smaller than that induced by the injection of dextrose, with consequent parallel diminished effect on the skin. Then, too, it required at the most four to five minutes to remove tissues for a biopsy, a period much shorter than the latent period required for the sugar level in the skin to follow that in the blood.

The influence of the interval between the removal of the biopsy specimen and the determination of its sugar content was studied. It was found that if the determinations were done within thirty to sixty minutes, little difference resulted when the skin remained at room temperature. In the experiments just reported, however, chemical analyses were always begun soon after the removal of the skin.

I agree with Dr. Kulchar that there is an intrinsic metabolism of sugar in the skin. I do not believe, however, that at the present time there is sufficient evidence to show that the skin has a special type of metabolism of sugar apart from that in all the other tissues. Lactic acid is present in the skin and probably comes from the glycogen. The mere presence of lactic acid, however, does not prove that there is a special type of metabolism present. Nor, in my opinion, would a parallelism in the sugar values of the skin and blood argue for a special kind of metabolism. If anything, that would indicate that the dextrose in the skin was there by diffusion from the blood.

I appreciate Dr. Kulchar's remarks in regard to the cutaneous sugar in pathologic conditions. I would rather not discuss that phase now, however, because the subject matter of the present paper includes only physiologic aspects.

THE "COMMON MOLE"

ITS CLINICOPATHOLOGIC RELATIONS AND THE QUESTION OF MALIGNANT DEGENERATION

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This study was undertaken with the hope that some of the rather confused and apparently controversial ideas about moles (nevi) and their relation to cancer and melanomas might be made more readily and more generally understandable. Although the literature is replete with reports on the "common mole," there is little definitely known of its origin, development and relation to melanocarcinoma, because both clinical and histologic opinions on the comparative innocence or malignancy of a particular lesion are often widely divergent. This is discouraging from a practical point of view, as the observer is faced with the unpleasant prospect of a grave prognosis and many uncertainties as to the future course of treatment of what is probably one of the most common growths in the skin. A more positive knowledge of the development and ultimate fate of these lesions is, therefore, essential in order that their removal, which is often solicited for cosmetic reasons, may not be attended by aggravation of the condition or even more distressing results. It seems to us that in view of the complete and in many instances incomplete destruction of thousands of "moles" by various means, there ought to be more precise information concerning their final outcome; yet the present fund of knowledge is not only fragmentary but also confusing, owing to opinions based largely on uncontrolled clinical impression. The facts that the question has repeatedly been asked, "What is the 'common mole?' " and that we have found it necessary to begin our article with a definition of terms indicate the need to clarify the fundamentals of the subject. It is probable that if there

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Drs. David L. Satenstein, Francis Carter Wood, James Ewing, Frank Fraser, Else A. Barthel and S. W. Becker gave helpful opinions on questionable slides.

were a uniform usage of accepted and clearly defined terms much difference of opinion would disappear and a clearer conception of the life cycle of the various marks which might come under discussion would be obtained. No two more unfortunate designations than mole and nevus can be imagined. From the beginning of this investigation it was apparent that a heterogeneous group of conditions was being included under the term mole, as used not only in the vernacular but also in medical parlance. In the first fifty odd lesions examined microscopically, there were eleven different conditions that had been designated clinically as the "common mole," and as the investigation was extended, other conditions were also found. Despite these difficulties, about 80 per cent of the first fifty lesions presented certain pathologic changes and, aside from minor variations in the anatomic features and certain differences in the gross clinical attributes, could be regarded as members of a single category. These lesions were characterized by the intracutaneous arrangement of nevus cells in typical configurations, such as nests, bands or strands. Kaiserling [1] pointed out that these remarkable collections of cells are recognized chiefly by their position and grouping rather than by their structure, which is variable. Though the appearance presented by these cells may vary a great deal, there is usually no difficulty in recognizing them, and they serve as the common denominator of a host of conditions for which such clinical terms as mole, soft nevus, cellular nevus and benign melanoma have been employed. Aside from the disadvantage of a multitude of names, some of the terms used are objectionable, though they enjoy the sanction of common usage, and it will be our endeavor to define these designations more accurately or give reasons opposing their employment in the nomenclature.

Nevus.—The term nevus has been used to describe a circumscribed deformity (of the integument) of embryonal or evolutional origin, which may be congenital or which may appear at any subsequent period during the patient's life.[2] This is a designation applied to a host of conditions seen at birth or shortly after. The English formerly restricted this name to the congenital vascular lesions, thus representing a usage that has not met with universal approval. The presence of the so-called nevus cells characterizes but one type of nevus for which we desire to restrict the designation mole or common mole. On the other hand, a type of lesion that we should like to call the potentially malignant melanoma may also occasionally appear early in life and therefore

1. Kaiserling, C.: Naevi (Pathologische Anatomie), in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 12, pt. 2, p. 600.

2. Darier, J.: A Text Book of Dermatology, Philadelphia, Lea & Febiger, 1920, p. 664.

may be classified clinically as a nevus; malignant changes in this type of growth should not be designated as nevocarcinoma for reasons that we will point out later. It is commonly observed that a single patient may show several or many varieties of nevi. These need not necessarily have the same origin; for example, there may be a so-called "common mole" on the face, Recklinghausen's disease on the trunk or/and an angioma on the limbs. In addition, several types of abnormalities may be found in a single growth, an example of which is shown in case 3. The term nevus, therefore, includes many types of lesions and of itself provides no clue as to the nature of the pathologic change to be expected. The designation pigmented nevus is a generic name applied to conditions having in common the occurrence of pigment, presumably melanin. The term pigmented mole, as commonly used, is a clinical designation applied to flat or raised lesions of various sizes and attributes, without implying anything as to the nature of the anatomic alterations. The expression nevus tardus, as it does not describe any specific type of mark and as many, if not the majority of, nevi are characteristically delayed in appearance or in development, is entirely superfluous, in our opinion.

Neuronevus.—As the name indicates, neuronevus refers to a nevus arising from nerve tissue. In this sense, therefore, some of the lesions observed in Recklinghausen's disease may be designated as belonging in this category. The term neuronevus is sometimes applied to the "common mole," which in accordance with Masson's belief is regarded as originating from nerve elements. It is difficult to state at the present time what types of growths deserve to be placed in this category, but it is essential that all lesions labeled in this manner be demonstrated beyond cavil to be composed of nerve tissue or its derivatives.

Fibroma Molle, Soft Fibroma and Naevus Fibromatosus.—These terms should be restricted to lesions characterized clinically by softness and pathologically by proliferating fibroblasts (connective tissue). There is a tendency for pathologists to diagnose such growths as neurofibromas, particularly if the cells are arranged in whorls. These growths, when situated on the face, may in some instances simulate the "common mole." The statement is often made that fibrosis represents an end stage of the ordinary mole, but our studies thus far afford no evidence favoring this view, although our material comprises lesions varying in duration up to thirty and forty years. It is possible that inflammatory fibrosis may occasionally be encountered in growths that have been traumatized, but this does not represent a true fibroma (case 7; possibly the report of case 6 may also be read in this connection).

Soft and Hard Nevi.—There are usually two general types: (1) the soft nevus, characterized by nevus cells in the cutis, by virtue of which the lesion is soft, and (2) the hard nevus, in which the essential altera-

tions reside in the epidermis. When the stratum corneum is thickened, the name keratoid nevus of Unna has been applied; when the layer of prickle cells is increased in thickness, the term acanthoid nevus has been used. Both layers may, however, be simultaneously affected, and the attribute of firmness is regarded as dependent on the pathologic changes in the epidermis. In a general way this division may be useful, but there are numerous exceptions and transitions. It is our belief that these clinical attributes cannot be employed as a means of classification. It may, however, be accepted that the pure hard nevus, affecting only the epidermis, has of itself no relation to the "common mole" or, probably, to the melanoma. In case 4 there was a lesion that was clinically firm; yet in addition to the epidermal changes, nevus cells were also found. The growth was the counterpart of the large pigmented lesions that are commonly called "bathing trunk nevi." Since the "bathing trunk nevus" has been described as occasionally having suffered malignant development, this case may be of interest from that standpoint.

Cellular Nevus.—This term is applied to growths showing nevus cells, but as other types of congenital abnormalities in the skin may also reveal a variety of cellular collections in the cutis, there is a possibility that the meaning of this term may be distorted. The designation has less objection if it is understood to connote those lesions which contain only nevus cells as the pathologic criterion.

Mole.—Unfortunately, popular usage has fixed the term *mole* in nomenclature. As it would be difficult to eradicate it and as it has been a source of confusion, it seems pertinent to define its meaning more precisely. By definition, then, the mole is regarded by us as a cellular nevus characterized histologically by the intracutaneous arrangement of nevus cells in special configurations (nests, bands and strands). Nearly all such lesions show the presence of a variable amount of melanin pigment both clinically and histologically, but this observation is not obligatory. These growths may be present at birth or appear shortly after birth or later in life. While an examination of our sections threw no light on the precise derivation of the nevus cells, there was, on the other hand, no definite evidence that the cells arise from the epidermis, as originally claimed by Unna.[3] As will be shown, our studies thus far indicate that the "common mole" differs from the malignant or potentially malignant melanoma. This does not mean that the "common mole" and a malignant melanoma may not occur in different lesions in the same subject, as in a case under our observation, nor that a malignant melanoma may not complicate a preexisting intracutaneous mole.

3. Unna, P. G.: Die epitheliale Natur der Naevuszellen, Deutsche Med.-Ztg. **18**:505, 1897.

which is an extremely rare occurrence but which we believe may have been taking place in case 15 (intradermal nevus in combination with an early nevus of the junction type). Authentic instances of the last-named combination are uncommon; when encountered, therefore, they should be recorded in the greatest detail. Dr. Satenstein has observed a number of such cases.

Melanoma.—The pigmented mole has been designated benign melanoma by some, for the purpose of contrasting it with the type of growth (malignant melanoma) that shows dangerous attributes, such as recurrence and metastases. The distinction can be considered satisfactory only by those who regard the former lesion as a not uncommon precursor of the latter. There are many observers who remain unconvinced that adequate proof of such transformation has been presented. We are among those who consider the term objectionable as used in this sense. Moreover, the medical public is apt to become overly uneasy when the designation melanoma is incorporated into any diagnosis, even if the prefix benign is appended, owing to the dissemination of much confused information as to the final outcome of such lesions. It is our belief that the type of lesion giving rise to malignancy has features of a clinicopathologic order that permit differentiation from the "common mole" (see definition), though it is realized that this distinction cannot be easily established in every case. We prefer to restrict the term melanoma to a lesion that is thought to be potentially or actually malignant. It is true that a growth may be cancerous from the start, but there are numerous instances in which our present histologic methods are wholly inadequate to determine this point and the condition becomes evident only by the later course of events. It is essential, therefore, to seek data based on other features, such as follow-up observations.

By a potentially malignant melanoma we mean a lesion which has the ordinary clinical attributes of a growth known to become malignant if tampered with or situated at a site likely to be a source of chronic irritation but in which the pathologic study shows no apparent evidence of activity in the cellular elements or local spread at the time of examination and perhaps only slight evidence of a surrounding inflammatory reaction. It is also requisite that the origin of the tumor be demonstrated as at the epidermodermal junction, though for the present our studies do not justify any assumptions as to the exact nature of the cell in the lower layer of the epidermis which gives rise to the growth. There is evidence that this origin is more easily demonstrable in the potentially malignant melanoma in which a secondary process, such as ulceration, hemorrhage or local growth, does not obscure this feature. It is therefore essential to study sections from many portions of the lesion for the purpose of determining the primary site. The potentially

malignant melanoma may be present from birth and hence may be designated clinically by some as a quiescent nevus or as a mole. There is evidence that such lesions may remain quiescent for many decades or even throughout life, especially if they are not exposed to trauma or other influences. It is, however, with such lesions that tampering, incomplete removal or chronic irritation is probably fraught with grave danger of active spread and metastases. We are still ignorant as to the incidence of such malignant change or the precise conditions under which this alteration takes place. The vast majority of such growths are smooth and devoid of hair, show a great variety of colors, including brown, blue and black, and usually are found on the extremities, especially the lower ones, though other sites, particularly the face, may also be affected. This is the type of lesion that may be diagnosed pathologically as benign and yet manifest itself later in the form of metastases, especially if incompletely removed. It is our belief that incomplete treatment of these growths by electrolysis, desiccation, coagulation or surgical removal is a dangerous procedure which may be followed by dire results. If our premises are correct, this type of lesion offers a hope of cure based on the complete prophylactic removal, provided metastatic foci are not present. While it is sometimes impossible to forecast whether metastasis has occurred, it may be put down as a cardinal rule that whenever the lesion shows suspicious characteristics or deviations from the normal (such as rapid increase in size, ulceration and bleeding), it should be removed widely. The growths that we have designated as junction type nevi represent what we consider potentially malignant melanomas (cases 10, 11, 12, 13, 14, 15 and 16).

Malignant Melanoma.—According to our views, the malignant melanoma is always a carcinoma, though the pathologic alterations may closely simulate a sarcoma in appearance. An advanced lesion of this type offers little hope for a complete cure except in variants which tend to run an exceptionally slow course. Such conditions require radical treatment in the hope that metastases, which may not be apparent, have not occurred or are of restricted distribution.

Nevocarcinoma.—This term should be applied only to that variety of growth in which these criteria are satisfied: (1) proof of the previous existence of true (intradermal) nevus cells and (2) proof that these cells have acquired cancerous properties. There are occasional observers who believe that the nevus cells do not undergo malignant change but that this complication occurs only in cells at the epidermodermal junction, the origin of the cells being unknown at present. Our observations are in accord with this view. It is our belief that such lesions are potentially or actually malignant melanomas, often superimposed on an ordinary intradermal mole, and that complication is

exceedingly uncommon. A biopsy specimen taken from one part of such a growth may show only the banal changes of the "common mole;" yet another area of the same tumor may reveal alterations at the epidermodermal junction which we regard as the precursor of the malignant melanoma. There is reason to believe that when this combination occurs, the tumor presents distinctive characteristics. When such a change is suspected, incomplete removal or taking repeated biopsy specimens are procedures to be avoided. The label nevocarcinoma should not be applied to malignant pigmented growths merely because they arise from lesions existing at birth or in early life; for example, the pigmented marks seen on the soles early in life are regarded by us as the precursor of melanocarcinoma, and we believe that such lesions, if examined at inception, would show evidence of alterations at the epidermodermal junction. We have sought for lesions located on the lower extremities which might be catalogued as genuine intradermal moles, but our search thus far has been fruitless; it appears, therefore, that these regions are rarely the site of the "common mole" in the sense in which that lesion has been defined in this paper. This is an interesting and practical point, for the answers to our questionnaire clearly indicate that the vast majority of malignant pigmented growths have been found on the lower limbs. It may be argued that the "common mole" in this situation acquires new properties by virtue of the traumatic element to which it is constantly exposed; yet there were at least two points at variance with such a hypothesis: (1) We examined a lesion of relatively short duration (case 13) in which the pathologic changes were those of a junction type nevus or of a potentially malignant melanoma; (2) the factor of trauma is by no means negligible in the case of the ordinary mole on the face. Women frequently pluck hairs. A history of bleeding or infection in such growths is common. It is probable also that washing the face and rubbing with a towel several times a day cannot be considered a negligible source of trauma. Men frequently nick the lesions in shaving, and bleeding is not uncommon. Irritation may also occur in patients with a superimposed inflammatory eruption, as in acne vulgaris. Yet we have been unable to find a single lesion in which we could be certain that malignancy had supervened under such influences. In addition, we knew that innumerable such moles are incompletely removed because destruction of the cells below the level of the skin would result in a disfiguring pit. For this reason and because experience has shown that it is not dangerous to do so, we have not completely destroyed the base of such growths, and yet no untoward results have ensued.

Lentigines.—The literature concerned with this subject is not only confused but also somewhat contradictory. Few observers are agreed on the clinical and pathologic nature of these lesions. Our material con-

tains too few examples to warrant a definite expression of opinion; yet a brief critical analysis may be useful. It appears that there are three types of lentigines.

1. Superficial lentigines. The superficial variety simulates the ordinary ephelis, but it is differentiated clinically by its lack of definite relation to such external factors as exposure to sun and pathologically by evidence of epithelial proliferation in excess of that seen in ordinary pigmented spots, for example, those observed in Recklinghausen's disease. The peculiar epithelial proliferation appears to involve the cells in the epidermodermal junction, chiefly the so-called clear cells in the elongated pegs where the appearance of pale projecting bulbs is created. An example would be furnished in the case reported by Zeisler and Becker.[4]

2. Deep lentigines. The deep lentigines show more elevation clinically and a greater degree of activity at the epidermodermal junction. There is evidence of an inflammatory reaction in the cutis, although this may not be pronounced. An example of this type is furnished, in our opinion, in the case described by Ebert.[5]

The superficial and the deeper lentigines are usually multiple and generally occur in children. It is possible that the milder changes are susceptible of complete regression. It was recognized by Pollio,[6] with whose opinion we are in accord, that the cells involved in the formation of lentigines are different from those seen in the ordinary intradermal nevus. It is our belief that the former lesions are probably potentially malignant melanomas, peculiar only in a number of clinical attributes. It is interesting that in the original presentation of Ebert's[7] case the following comments were made:

> In the very early lesion from which I secured a section there is a marked round cell reaction about the vessels around the lesion, and that is histologic evidence of the possibility of malignant change. . . . Dr. Jaffé looked at the section, and from what his associates said I understand that he considered the condition, histologically at least, as potentially malignant.

3. Lentigo maligna. These spots are usually, but not necessarily, found in old persons, and their tendency to form cancerous growths is indicated by their name. We are of the belief that such lesions if examined at inception would show changes at the epidermodermal junction

4. Zeisler, E. P., and Becker, S. W.: Generalized Lentigo: Its Relation to Systemic Nonelevated Nevi, Arch. Dermat. & Syph. **33**:109 (Jan.) 1936.

5. Ebert, M. H.: Multiple Pigmented Nevi: A Study of the Origin of the Nevus Cell, Arch. Dermat. & Syph. **37**:1 (Jan.) 1938.

6. Pollio, G.: Ueber Pigment-Naevi, Arch. f. Dermat. u. Syph. **80**:47, 1906.

7. Ebert, M. H., and Wolf, M. J.: Multiple Epithelial Nevi, Arch. Dermat. & Syph. **29**:765 (May) 1934; Multiple Nevi, ibid. **30**:292 (Aug.) 1934.

analogous to the deeper types of lentigines seen in the younger age group. In all likelihood the melanotic whitlow belongs in this category or a related one. When Miescher [8] wrote of melanocarcinoma as being derived from lentigines, he referred probably to lentigo maligna, and his several accounts indicated that he observed no essential differences between this type of malignant growth and that occurring on the basis of nevi. So-called lentigo maligna, in the opinion of Satenstein,[9] is probably of two types, (1) the superficial junction type nevi and (2) seborrheic keratoses becoming malignant.

When these various types of growths show evidence of malignant change, it is erroneous to designate them as nevocarcinoma according to the criteria laid down in this paper, for it is our belief that these alterations do not concern the ordinary nevus cell as observed in the intradermal mole. There is a scarcity of evidence to indicate that the process of *Abtropfung,* which in our opinion characterizes the potentially malignant melanoma, is the real source of nevus cells in the cutis, notwithstanding superficial resemblances, their common origin in early life and the rare instances illustrating a combination of both lesions. In agreement with the opinion expressed by Kaufmann-Wolf [10] and others, the genetic process at the epidermodermal junction is regarded as potentially malignant (precancerous), whether it arises early or late in life. At present nothing is assumed as to the precise nature of this process, though the evidence appears to point to implication of the clear cells in the lower part of the epidermis; the relation to the so-called dendritic cells remains to be determined.

A second point that this investigation leads one to stress is the difficulty frequently encountered in deciding the differential clinical diagnosis between the "common mole" and the many small tumors of the skin with which it may be confused. As has already been mentioned, in the first fifty specimens studied there were eleven different growths that either had been or could have been confused with this type of nevus. A tiny nodular basal cell epithelioma certainly must cause frequent error, and this probably accounts at least for some of the reports of moles terminating in basal cell epithelioma. We have observed a number of cases of such an occurrence and included in our series is a patient who presented several lesions, of which one was desiccated as a "common mole" and another, microscopically examined, proved to be a trichoepithelioma (case 8). It is possible, though it no longer could be proved, that the lesion taken for a mole in this case might actually have been a

8. Miescher, G.: Melanom, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 3, no. 2, p. 1005.

9. Satenstein, D. L.: Personal communication to the authors.

10. Kaufmann-Wolf, M.: Beitrag zur Kenntnis der präcarcinomatöse Alteration bei pigmentierte Naevi, Arch. f. Dermat. u. Syph. **144**:73, 1923.

trichoepithelioma. As nevus cells were not found histologically in any of the growths which proved to be epitheliomas, we cannot assume that in our cases such a transition actually took place. Other conditions, further illustrating this diagnostic difficulty, are described in the detailed classification of our cases.

Before undertaking this investigation, we felt that it would be useful to have an expression of opinion on certain points from a group of American dermatologists as a basis for future comparison. A questionnaire was therefore submitted to about one hundred and twenty members of the American Dermatological Association. The questions proposed were: 1. Have you ever seen a small common hairy mole become malignant? 2. Have you ever seen a histologically proved benign cellular nevus (mole or pigmented mole) become malignant subsequently? The data furnished on the basis of ninety-three answers not only proved interesting but reflected the confusion of ideas attending this subject; hence a brief analysis of them appears warranted. Of the ninety-three dermatologists, eighty-five had not observed malignant change in a small common hairy mole, despite manifest opportunities to witness such transformation. In addition, this group has never seen a histologically proved benign cellular nevus (mole or pigmented mole) become malignant subsequently. It is realized that biopsy specimens are rarely taken in such cases in private practice and that this procedure is more commonly carried out in dispensaries and hospital services. It is important, therefore, that of the dermatologists in this group, many had access to a tremendous amount of pathologic material. When it is further considered that many of these lesions have been subjected to daily irritation or to the trauma of complete or incomplete removal, these statistics are most noteworthy. The statistics supplied by the questionnaire, which was apparently correctly understood, completely refute the erroneous idea generally prevalent that the "common mole" is attended not infrequently by cancerous degeneration. The result of the examination of the numerous specimens comprising the basis for this report entirely substantiates the idea of the exceedingly great rarity of cancer as a complication or sequel to the "common mole" (intradermal nevus).

The few members who reported a change to malignancy described growths that were smooth, bluish black or steel blue, devoid of hair and generally situated on the extremities, especially the lower. One observer mentioned a case in which the lesion occurred on the arm and contained a few tiny hairs, but in his opinion "This was not a true hairy nevus in the accepted sense." Another stated that in his experience the blue-black or steel blue mole was the precursor of malignant melanoma; yet he added that in his opinion "The common practice of pulling out hairs from the ordinary pigmented nevus or the occurrence of slight secondary infection from a variety of causes might stir up such a lesion." He

was, however, willing to admit that the constant nicking, as in shaving over his own moles, had not been a competent producing cause. These observations seem to illustrate one of the common inconsistencies prevalent, for the blue-black or the steel blue growths which are generally accredited with developing into the metastasizing melanoma are lesions usually devoid of hair, certainly of coarse hair. While pigmented nevi with hair (the hair being an essential part of the nevus) may under exceptional circumstances produce malignant melanoma, the occurrence appears to be rare. Another observer expressed the belief that the pigmented hairy nevus might become malignant, but only in the same sense that normal skin might become cancerous after chronic irritation—a viewpoint becoming more and more generally accepted. A few had seen clinically benign pigmented lesions undergo malignant change, but it is our surmise, from the few details furnished, that they were the smooth brown, bluish black or slate blue growths and, perhaps also, the rare relatively nonpigmented melanoma. Others, noting the same sequence of events, were doubtful that such lesions had been benign from the beginning in the pathologic sense (Brunsting). On the other hand, one observer had encountered conditions diagnosed as malignant on the basis of microscopic examination (we do not know whether a dermatopathologist or a general pathologist was responsible for this opinion), yet clinical observation appeared to indicate that the growths were benign. This occurred repeatedly in our series also, and not infrequently three or four outstanding dermatopathologists differed in opinion. In an isolated instance mentioned in another reply to our questionnaire, half the lesion appeared benign, whereas the remainder was malignant. A follow-up letter asking for further details failed to supply a complete clinical description of the case together with the pathologic changes present on which the diagnosis of malignancy was based. At the other extreme was the following statement made by one of the physicians, "Most of the fear of malignant degeneration following removal by coagulation or desiccation is either pure hysteria on the part of misinformed general practitioners or propaganda on the part of the surgeon who wants to excise these growths." In perusing a complex literature, especially that found in surgical journals, it is evident that surgeons as a group have contributed greatly toward the confusion. A notable exception is Affeld's paper,[11] which is based on a clinicopathologic correlation; it is interesting that in a study of 266 instances of malignant melanoma he did not encounter a single example arising from a hairy mole.

What determines the change from a benign to a malignant process? Is it trauma? Or does trauma play only a minor role, the essential

11. Affeld, D. H.: Melanomas, Am. J. Cancer **27**:120, 1936.

motivating factor being unknown? In the development of malignant melanoma, trauma without a doubt is the precipitating factor in some of the cases, the exact percentage of which it is most difficult to determine, as the point hinges somewhat on the reliability of the history or on supposition or theory. Trauma is credited with playing a part in a number of cases reported by Gleave, Amadon, Coley and Hoguet, Stevenson, Hazen, Farrell, Klauder and others.[12] More than 50 per cent of the conditions occurred on the feet, which in itself is somewhat suggestive. The next most common site, the head, is also a part particularly liable to injury.

In many of the specimens that were studied, considerable difference of opinion arose as to whether the process was benign or malignant. For instance, if "trickling off" (*Abtropfung*) and segregation are essential alterations that may be seen in either a benign or a malignant lesion, it may not be unreasonable to suppose that the factors responsible for these phenomena in a benign mark may, through local irritation or stimulation, be changed to give rise to a malignant one. Some vital agent must still be discovered, however, to account for subsequent events, namely, extension of the tumor, metastasis or the occasional rare regression or complete spontaneous disappearance of growths, such as have been recorded in the literature.

Kreibich [13] described a case of melanotic nevocarcinoma combined with melanotic lymph gland tumor in a man of 50. The nevus itself was not affected by the tumor. Histologically, extensive degeneration of the epithelium with "trickling" (Unna) of the epithelial cells into the cutis was found. The author distinguished two forms of epithelial "trickling," a benign one, as in nevus, and a malignant one, as in melanocarcinoma. The relation to Paget's disease was mentioned. He called attention to the fact that simple pigmented nevi (i. e. smooth, nonwarty and nonhairy) were more disposed to the development of carcinoma than were cellular pigmented nevi (intradermal nevi), a point that we wish to emphasize.

The exact significance or correct interpretation of epithelial "trickling" is therefore of the greatest importance, not only from the standpoint of the origin of nevi but from the point of view of malignant activity as well. According to Miescher,[8] "trickling off" occurs slowly and only in a few small areas in nevi, so that it has to be looked for diligently; but in malignant melanoma it forms the principal element of the picture. Our so-called junction type nevus (group 3 and figs.

12. Farrell, H. J.: Cutaneous Melanomas, Arch. Dermat. & Syph. **26**:119 (July) 1932.

13. Kreibich, C.: Ueber Naevuscarcinom, Arch. f. Dermat. u. Syph. **130**:542, 1921.

12 to 20) can be recognized by the "trickling off" of cells and also by the presence of the clear or embryonic cells, which may resemble the Paget cell and which represent probably changed epidermal cells. Great difference of opinion exists as to the origin of the cells.

It is interesting to note that our group of junction nevi seem to fall into two categories: (1) those in which the original lesion is observed early in infancy (congenital) and (2) those in which the mark appears about puberty or in adult life. In our collection of cases the latter type was more common, and, in addition, the lesions were of comparatively recent origin, i. e. two months, three months, six months, three years and six years, respectively, in 5 of our cases (not to mention others). In adults showing lesions of such short duration, the question arises whether they should be considered as of nevic origin (hence, originally benign). Microscopically the lesions showed changes apparently indistinguishable from those seen in the first (congenital) group, in which the factor of trauma or irritation seemed to play an important part in their further development. It appears, then, that the histologic characteristics cannot be used as the sole criterium for determining origin or prognosis. The apparent difference in frequency of occurrence and prognosis between the congenital and the delayed or acquired types of junction nevi has been noted also by Pack,[14] who "in a careful clinical investigation found that the average person has at least twenty pigmented spots. These spots are important because they may cause disfigurement or become malignant. Five patients with undoubted congenital nevocarcinoma were alive and well without recurrence of the condition, 2 for five years, 3 for two years and 1 for one year after treatment. Of the 20 with acquired conditions, 15 were dead. While we consider the junction type nevi as potentially malignant, it would appear, from our observations, that like other so-called precancerous lesions they need not necessarily terminate in malignant melanomas. This is true at least for the relatively short time we have been able to keep our patients under observation and seems to be particularly the case with marks of the congenital junction type, the latter having therefore a much better prognosis.

Unna[3] many years ago called attention to a phenomenon in the epidermis overlying nevi, namely the appearance of cavities containing free epithelial cells. Unna stated the belief that these free cells gradually find their way to the cutis (*Abtropfung*), where they are transformed into nevus cells. Darier[15] found this phenomenon in two

14. Pack, cited by Adair, F. E.: Treatment of Melanoma: Report of Four Hundred Cases, Surg., Gynec. & Obst. **62**:406, 1936.

15. Darier, J.: Des naevocarcinomes, Bull. Assoc. franç. p. l'étude du cancer **6**:145, 1913.

of nine nevi and in nine of nineteen primary nevocarcinomas. He called these collections of cells *thèques*. He definitely stated that they were present only in the primary tumors.

Nicolau [16] recently contributed his own observations on a case of nevocarcinoma with numerous metastases. In a number of these metastatic tumors, he found in the more advanced masses and occasionally in the hair follicles and rete pegs some cavities (thèques) containing larger or smaller numbers of free cells showing no intercellular filaments. From these results, Nicolau argued that the original conception of Unna of the role of these free cells in the genesis of nevi and nevocarcinoma must be revised. He stated the belief that the free cells originated from the tumor and were in reality an intraepidermal metastasis. From a study of the histologic preparations, it appeared that the cells reached the epidermis one by one and by division formed a small mass, which was finally extruded by normal exfoliation.

Darier,[17] commenting on the aforementioned statement of Nicolau, stated the belief that there was no question but that the histologic changes noted by the latter were identical with those noted in primary tumors by Darier. Nicolau, however, laid no stress on certain changes in the cells of the basal layer which to Darier were of capital importance, since they were in his opinion the starting point of the entire process. Hence he rejected Nicolau's conception of a migration of neoplastic cells into the epidermis. In Darier's opinion, the close approximation of the neoplasm caused changes in the basal cells which led to the formation of *thèques*. This seemed the most plausible explanation of the process, though admittedly it was purely hypothetic. Recently Becker,[18] Satenstein and others have stressed the epidermodermal junction as the probable starting point of the process. This appeared to be true of the specimens we studied, especially as our series included only those lesions which were considered to be early.

CLINICAL AND PATHOLOGIC CLASSIFICATION

As stated previously, about 80 per cent of the marks examined in our series fitted into the category characterized by the arrangement of nevus cells intracutaneously in nests and strands. Histologically this represents the type that has been designated as the intradermal nevus.

16. Nicolau, S.: Sur le phénomène de migration cellulaire intra-épidermique dans le naevocarcinome (à propos de l'étude des tumeurs de métastase), Ann. de dermat. et syph. **1**:746 (July) 1930.

17. Darier, J.: Note sur les cellules du naevocarcinome. Leurs migrations et leurs propriété cancérigène (à propos du mémoire du Prof. Nicolàu) **1**:763 (July) 1930.

18. Becker, S. W.: Cutaneous Melanoma: A Histologic Study Directed Toward the Study of Melanoblasts, Arch. Dermat. & Syph. **21**:818 (May) 1930.

The "common mole," according to our conception, is one of several examples of an intradermal nevus. It is unfortunate that the intradermal nevus has so many varied clinical types. This type of nevus exceedingly rarely gives rise to cancer or to malignant melanoma. If the malignant condition occurs, which is exceptional, it is probable that the nevus is not a pure intradermal type but represents a combination referred to in group 4.

As moles (nevi) must in the last analysis be classified on the basis of their histologic structure, the following classification is suggested:

1. *Intraepidermal Nevus.* This is essentially a clinical type, as histologically no nevus cells are found, and only the history and clinical picture suggest its nevic origin. Marks which may be clinical examples are:

   (*a*) Naevus verrucosus (hard warty nevus)
   (*b*) Naevus verrucosus linearis (linear warty nevus)
   (*c*) Naevus papillomatosus (a bad designation, as it probably generally refers to a soft warty nevus, which would place it in group 2)

2. *Intradermal Nevus.* Marks which may be clinical examples are:

   (*a*) Verruca mollis, soft wart or cellular nevus (the "common mole")
   (*b*) Naevus papillomatosus (group 1)
   (*c*) Lentigines, deep (?) (the so-called beauty mark seen frequently on the face)
   (*d*) Naevus pigmentosus et pilosus (pigmented mark with hair)
   (*e*) Naevus pigmentosus et verrucosus (soft warty pigmented mark)
   (*f*) Naevus pigmentosus et pilosus et verrucosus (combination of pigmented hairy and soft warty mark)

3. *Junction or Borderline Nevus.* Marks which may be clinical examples are:

   (*a*) Naevus spilus (small smooth flat pigmented spot)
   (*b*) Naevus pigmentosus
   (*c*) Lentigines (1) superficial, (2) deep

   Clinically may be indistinguishable from those which microscopic examination would place in another group

   (*d*) Naevus pigmentosus et verrucosus (exceedingly rare; when it occurs it may represent a combination type [case 15])
   (*e*) Naevus pigmentosus et pilosus (exceedingly rare)

4. *Combination Type Nevus.* Histologically it exhibits a combination of one or more of the three types already mentioned. Clinically it assumes the characteristics of one or several of the previously mentioned varieties.

5. *Blue Nevus.* This, fortunately, is a histologic as well as a clinical designation. Clinically the mark is probably often mistaken for a slate black mole (malignant melanoma).

A brief description of the histologic classification seems necessary.

1. Intraepidermal nevi lie entirely within the epidermis and present a proliferation of normal epithelial cells, a mixture of prickle and basal cell type, not referred to as nevus cells. They may or may not be pigmented. They rarely terminate in cancer.

2. Intradermal nevi are probably the most frequently encountered lesions and are characterized by the occurrence of nevus cells arranged intracutaneously in nests and strands. The cells are of the mature type, and to become malignant they revert to the embryonic type. Pigment is generally present in varying amounts. Cancer or malignant melanoma rarely, if ever, occurs.

3. In junction type nevus (Satenstein) or borderline melanoma Becker [18] stated: "The process may be interpreted as hyperpigmentary due to an increased number of melanoblasts at the epidermo-dermal junction." The cells are not separated from the epidermis, as in the intradermal nevi, in which the nevus cells are seen in nests or strands usually detached from the epidermis. The cells in this type are of the embryonic (anaplastic) type, and the lesion constitutes the forerunner of the malignant neoplasm. It is the lesion we prefer to call the potentially malignant melanoma. The criteria necessary to decide whether a junction nevus has definitely become a malignant melanoma require careful consideration of both the clinical picture and the course of the lesion, as well as a minute study of the histologic changes. Lesions are encountered which clinically seem innocent and which apparently pursued a benign course as long as we have been able to keep the patient under observation. But the reports on slides studied in these cases by various pathologists show great differences of opinion. If a report of malignant melanoma had been accepted in such cases without due consideration of the innocent clinical course, great harm might have been done. We believe that the clinical criteria for malignant melanoma have been sufficiently stressed so that it would be superfluous for us to restate them, but the histologic grounds or basis for such a diagnosis certainly seem less clearcut.

It appears logical that the following points are necessary for the diagnosis of malignant melanoma: (1) "trickling off" and segregation (development of *thèques*) (one of the principal changes and found without difficulty), (2) the presence of clear cells, which may resemble the Paget cells, (3) mitotic figures (generally readily found), (4) variably sized and shaped (large and small) pigment cells and (5) chronic inflammation. The more evident each of these changes appears in the section, the more certain one may be of the malignant nature of the growth.

4. The combination type nevus represents a combination of types 1, 2 and 3 (case 15).

5. The blue nevi (slate blue or grayish blue), which are chiefly found as isolated lesions on the face and dorsum of the hands, have no relation to melanoma. The color is apparently determined by the number and depth of the melanoblasts. It must be emphasized that the name blue nevus should be restricted to pigmented growths composed of a peculiar type of connective tissue cells apparently capable of forming melanin; that so far as the literature and our limited observations are concerned these spots are benign in their course, and that diagnosis on the basis of color alone is unreliable, as other lesions, such as the melanoma and the

"common mole," may reveal similar shades of blue. In rare instances [19] an ordinary intradermal mole may show clinical features apparently indistinguishable from those of the blue nevus; this phenomenon is apt to occur when the nests of nevus cells and their accompanying pigment are separated from the epidermis by a wide stretch of intervening connective tissue. It is interesting that a number of cases have been recorded in which the characteristics of an ordinary mole were associated more or less intimately with those of the blue nevus of Tièche.[20] This represents another example of a combination of nevi. It has been claimed that blue nevi may terminate in sarcoma, but such a change must be rare indeed, for Satenstein,[9] Becker, Peck, Ewing, Wood and Fraser [21] have not seen examples of it.

In our studies we included only 1 case of intraepidermal nevus, since this type was not related to the "common mole" or to the melanoma. Case 1, in which the growth typified the intraepidermal nevus, should, however, be recorded, because in one portion of the section the epidermis appeared to be invading the cutis, and it was Dr. Satenstein's belief that this represented an early stage in the formation of squamous cell epithelioma, which was the type of transformation to be expected in intraepidermal nevi. However, intraepidermal nevi are rarely complicated by cancer, this case being an exception rather than the rule.

REPORT OF CASES

CASE 1.—M. K., a woman aged 37, had had a lesion on her right cheek for the past nineteen years. In the past two years it had attained the size of a large pea. The growth was somewhat pedunculated, light brown, moderately firm and definitely verrucous. In the center there was a dried hemorrhagic crust, the probable result of recent trauma. The lesion was removed and the base desiccated. Healing was uneventful.

On microscopic study the chief changes were observed in the epidermis, all of its layers being hypertrophied. There was decided hyperkeratosis, which followed all the irregularities in the surface of the growth. At the point corresponding to the central hemorrhagic crust were areas of parakeratosis disposed unevenly and amorphous masses that probably represented the remains of old hemorrhage. There was decided acanthosis, and the basal membrane was intact except for a small area where the cells seemed to be penetrating the cutis. The lower layers of the epidermis showed moderate intercellular edema, scattered areas of intracellular edema, rare mitotic figures and a few leukocytes. In the immediately adjacent cutis there was a chronic and acute inflammatory reaction composed mainly of blood vessels, perivascular lymphocytes and a few polymorphonuclear leukocytes; in other areas there was a conspicuous increase in the number of blood vessels and fibroblastic cells, as observed in chronic granulation tissue.

The diagnosis was intraepidermal (hyperplastic) nevus with a lesion that apparently was an early stage squamous cell epithelioma.

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19. Sato, K.: Beitrag zur Kenntnis des "blauen Nävus," Dermat. Wchnschr. **73**:1073, 1921.

20. Tièche, M.: Ueber benigne Melanome (Chromatophorme) der Haut, "blaue Naevi," Virchows Arch. f. path. Anat. **186**:212, 1906.

21. Becker, S. W.; Peck, S. M.; Ewing, J.; Wood, F. C., and Fraser, J. F.: Personal communication to the authors.

CASE 2.—L. O., a woman aged 47, was observed April 15, 1936. There were two lesions on the face. The one on the left cheek had been present during her entire life. It was sessile, pea sized, fairly smooth and moderately firm and showed a mottled brown surface with many fine telangiectases. On several occasions it had bled after injury, but the precise nature of the trauma could not be ascertained. This growth was known to have antedated the appearance of the one on the opposite cheek, the latter having been present for some thirty-five years as a

Fig. 1 (case 1).—Intraepidermal (hyperplastic) nevus with what appears to be an early squamous cell epithelioma.

slightly smaller lesion which was moderately firm and the color of normal skin, with a definitely yellow overtone. Both growths had always been devoid of hairs, and in both an increase in size had occurred gradually.

The diagnosis was intradermal nevi.

Histologic examination of the growth on the left cheek (fig. 3) disclosed the typical changes of the "common mole." The epidermis was thin. The zone of nevus cells was separated from the epidermis by a layer of connective tissue containing many dilated capillaries. There were scattered deposits of pigment

Fig. 2 (case 2).—Two "common moles" of different size and color.

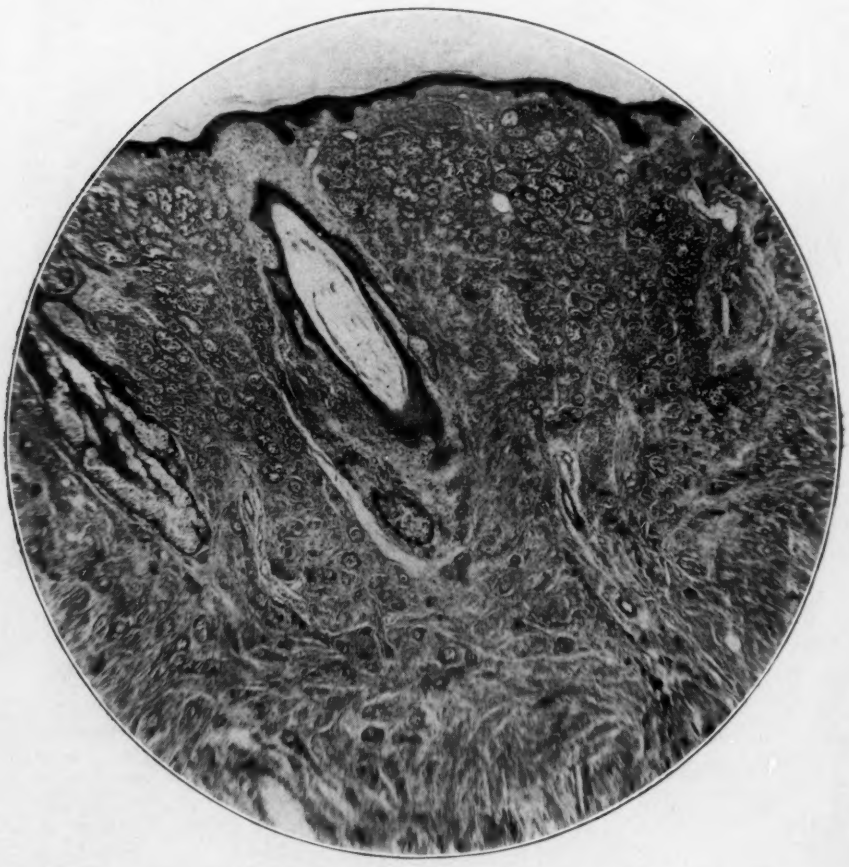

Fig. 3 (case 2).—Low power section of the intradermal nevus on the left cheek.

chiefly at the upper limit of the cellular infiltration. The nevus cells were arranged in typical groups, nests and strands. The sebaceous glands were relatively few or in a definite atrophic state, a condition that seemed to be caused by the mechanical pressure of the masses of nevus cells. There were a few hair follicles.

The minute anatomy of the lesion on the opposite cheek was essentially similar except that there were more sebaceous glands, which appeared to be fairly normal. It was our impression that the presence or absence of these structures may have played a part in determining the color of the growth by adding a bulk of sebaceous matter to the lesion.

Case 3.—A. D., a girl aged 14, was born with a small spot on the upper lip. The mother did not remember the color of the growth at birth, but hairs had always been present. It had grown slowly, reaching its present size about four years ago. The lesion extended from a point near the vermilion border of the upper lip to the left nostril. It was dime sized, pinkish brown and raised several millimeters above the level of the normal skin. The surface was irregularly pitted, and numerous hairs were present, many being coarse.

Fig. 4 (case 3).—A pigmented warty and hairy nevus fulfilling the requirements of the "common mole."

The diagnosis was intradermal nevus, with lymphangioma.

Microscopic examination showed masses of nevus cells throughout the upper and middle part of the cutis in the form of groups, nests, bands and some strands. The epidermis showed only thinning, probably due to the mechanical pressure of the infiltrate, and depressions corresponding to the follicular openings; the latter seemed to explain the clinical resemblance to an orange peel. Between the epidermis and the masses of nevus cells, there were greatly dilated epithelium-lined spaces. These, because they did not show the presence of red blood cells, were regarded as lymphatic channels (lymphangiectases); it is possible, however, that they were originally blood channels of congenital origin. The masses which were found in the major part of the cutis were composed of uniform cells showing small darkly staining nuclei, without visible cellular outlines. Pigment was not found in these sections, but its occurrence was noted occasionally when the studies were made only with the hematoxylin and eosin stain.

Case 4.—On the upper part of the right arm of a girl of 16 there was an oval hairy and verrucous blackish brown lesion. It measured 1½ by 1 inches

Fig. 5 (case 4).—Pigmented warty and hairy nevus ("common mole").

Fig. 6 (case 4).—Low power section of verrucous intradermal nevus.

(3.8 by 2.5 cm.) in the longest diameters. The numerous hairs were black and coarse. The growth had been present from birth and had gradually increased from a small spot to its present size. The patient believed, though she was not certain of the point, that the hairs had appeared only during the past seven or eight years. With the area under local anesthesia the lesion was excised, and the wound healed in two weeks.

On histologic examination the epidermis was found to be thrown into many papillomatous folds, due to the collection of edematous nevus cells. There was a thick hyperkeratotic scale which was responsible for the hard part of the lesion. The remainder of the epidermis was atrophied owing to the pressure of the masses of nevus cells. In many places there was a definite layer of connective tissue that separated the thinned epidermis from the groups of nevus cells and in intervening areas occasional clumps of pigment. There were many hair follicles which had

Fig. 7 (case 5).—Verrucous intradermal nevus. The rounded smooth mass near the upper center is a large hematoma that had been mistaken clinically for an early melanocarcinoma.

been cut at various angles. The nevus cells were diffusely arranged down to the deeper layers of the corium in the typical manner observed in an ordinary mole.

The diagnosis was verrucous intradermal nevus.

CASE 5.—A. Z., a woman aged 29, presented a naevus pigmentosus et pilosus et verrucosus of the elbow, the growth having been noted at birth. The large round smooth mass which looked like an early malignant melanoma developing on the original nevus was seen to be a hematoma on microscopic examination. This case illustrates a not infrequent clinical error.

The diagnosis was verrucous intradermal nevus with hematoma.

CASE 6.—S. C., an Italian woman aged 54, had a single growth on the left ala nasi of nine years' duration. It had apparently arisen on normal skin as a pimple, which had grown gradually to attain a length of almost 1 inch (2.5 cm.) and a breadth of ½ inch (1.3 cm.). The mass was soft and slightly lobulated and hung from a slightly constricted pedicle. The surface was mottled in appearance; in areas it had the color of normal skin, with interspersed dull white depressed spots

creating the effect of fine lobulations; in other areas it was reddish and bluish, with superficially coursing telangiectatic vessels. The growth was soft to moderately firm on palpation. There had never been any growth of hair, and it had bled frequently, especially when traumatized, as in the act of washing the face. It was removed by an elliptic incision, and the base, which bled freely, was cauterized.

On histologic study the epidermis was found to be thin, with a decided amount of pigment in the basal cell layer. The growth consisted of an edematous stroma containing many new blood vessels and lymphatic spaces. Occasional hair follicles were encountered at one edge of the specimen, but no collections of nevus cells.

It was the opinion of Dr. Satenstein that the lesion was an angiosarcoma. Several other pathologists regarded the lesion as a pedunculated fibroma. The histologic features were sufficiently unusual that a final diagnosis could not be given except to state that the growth was not a nevus despite its rather close clinical resemblance to the "common mole."

Fig. 8 (case 7).—Clinically this lesion was looked on as a "common mole," but on histologic examination was proved not to be intradermal nevus.

CASE 7.—Since birth, this patient, a man of 23 years, had had a small elevated pea-sized circumscribed nodule located at the root of the nose. The lesion had a peculiar dull white color, the paleness being accentuated by a surrounding group of minute comedos. The growth was firm, smooth and devoid of coarse hairs. There was no history of bleeding or of trauma.

Histologic examination showed that the epidermis was relatively normal. There were occasional prolongations of the rete pegs, which probably represented cross sections through the hair follicles cut on the bias. There were many clear cells in the basal layer of the epidermis and of the hair follicles, but no definite deposition of pigment. In the upper part of the corium there were numerous blood vessels. Scattered throughout the cutis there were many sebaceous glands, hair follicles and sweat glands. The upper half of the cutis contained an infiltration of what appeared to be typical fibroblastic nuclei, and the superior portion of the infiltrate showed scattered connective tissue cells containing pigment; the pigment was chiefly arranged in the form of fine granules, though some of it was also deposited as irregular masses. Van Gieson's stain revealed that the groups of fibroblast-like cells had but little intercellular substance taking the pink color of connective tissue. The Weigert stain for elastic tissue showed the persistence of small elastic

tissue fibers in several areas in the infiltrate, while in other places the elastic tissue fibers appeared to be swollen and broken.

We thought it possible that this growth might be a hystiocytoma, or tumor of connective tissue origin. Dr. Satenstein, on the other hand, stated the belief that it was a Recklinghausen tumor. Here again there was a difference of opinion regarding the histologic section. The lesion had been present as long as the patient could remember, and although it was clinically mistaken for a "common mole," the histologic examination proved that it did not belong in this category.

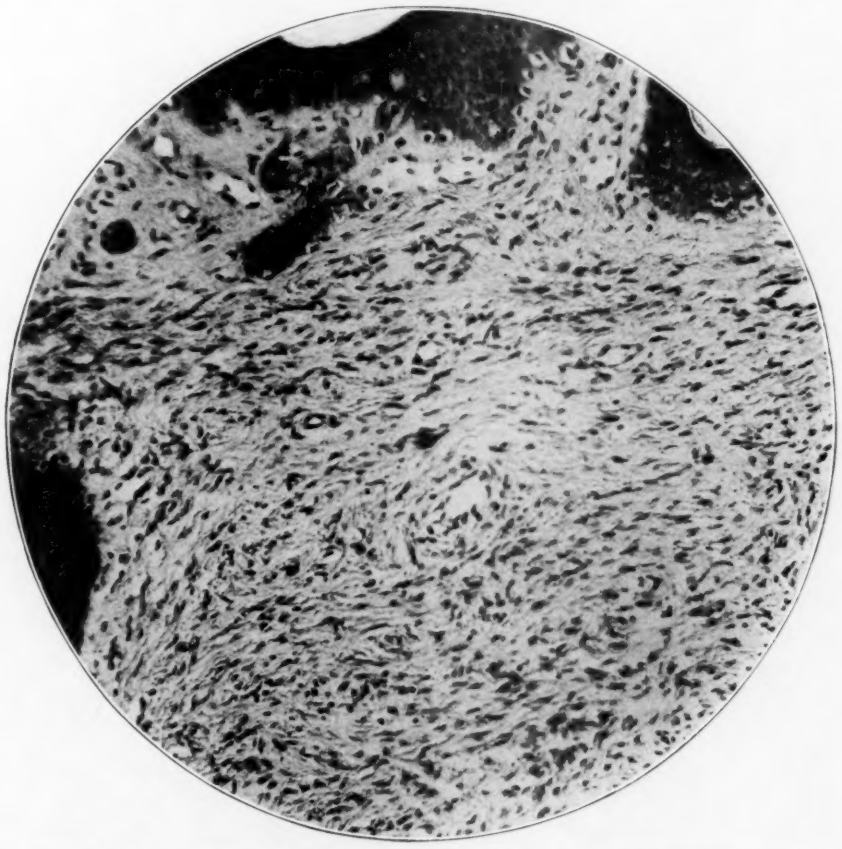

Fig. 9 (case 7).—Tumor of connective tissue origin? Recklinghausen's tumor?

CASE 8.—A. M., a man aged 63, had two lesions on the forehead, which had been present for many years. Both appeared to be smooth and free of hairs. The one on the right side was pea sized, soft and light brown and had not grown; as it seemed to show the attributes of a "common mole," it was destroyed by desiccation. The other lesion was slightly larger, somewhat firm and fleshy pink and was situated near the scalp line to the left of the midline. The center showed many irregular depressions. There had been a slight increase in size in the past two years. The growth was removed and the base desiccated. A cross section showed that the tissue was relatively firm and that it had a dead white color.

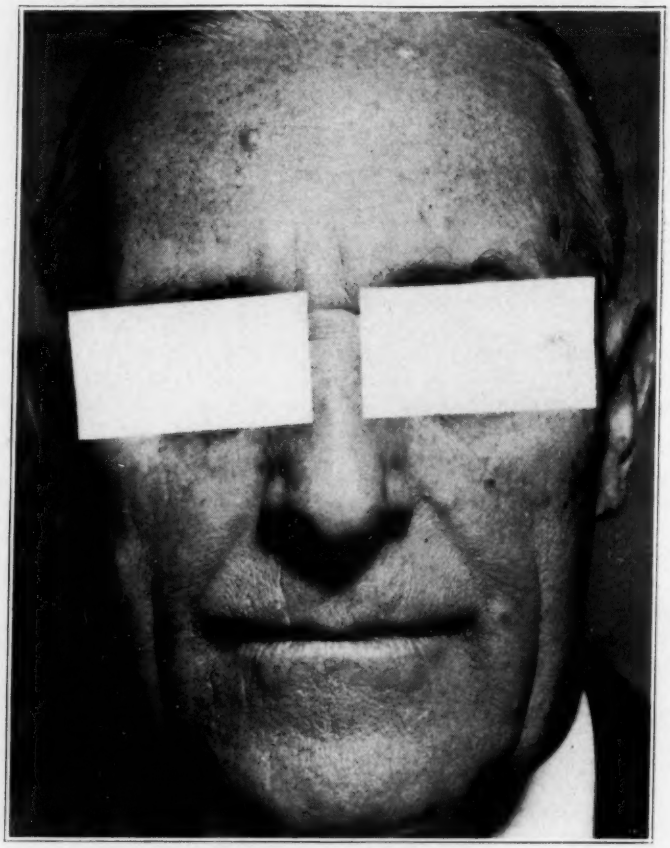

Fig. 10 (case 8).—Trichoepithelioma. Mistaken clinically for a "common mole."

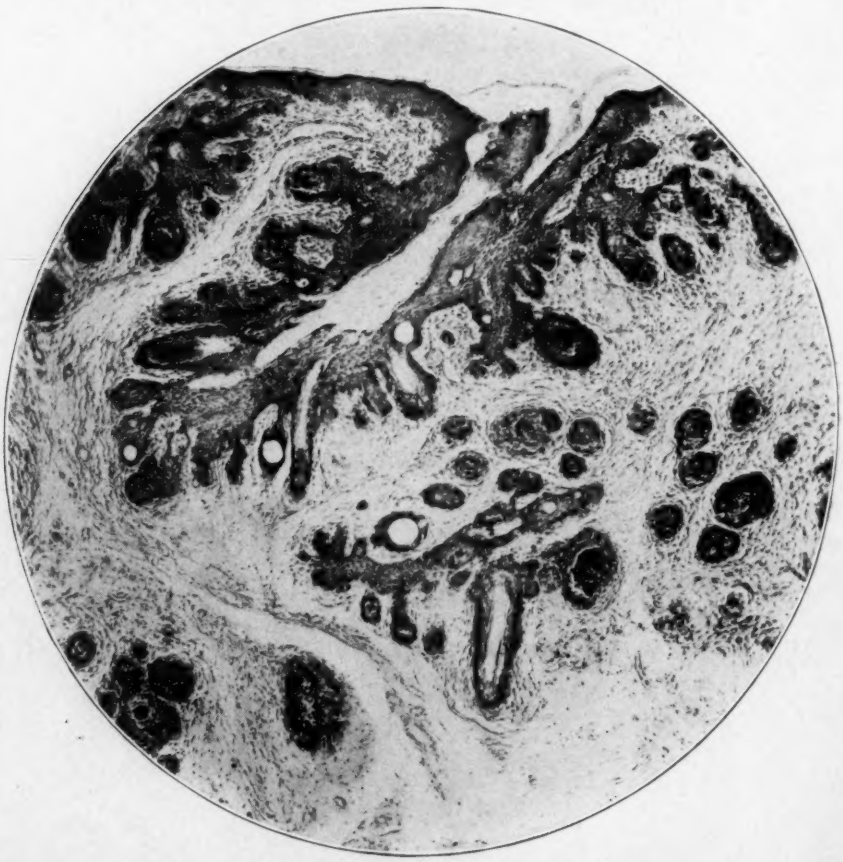

Fig. 11 (case 8).—Low power section of trichoepithelioma.

The diagnosis was trichoepithelioma, with its origin in the hair follicles. The central depressions were caused by dilatation of the follicular openings.

The nature of the first lesion destroyed, which had seemed to be an ordinary mole, must be reevaluated in the light of the microscopic observations of the second nodule. It appeared probable that growths of the nature of trichoepithelioma occurred more commonly than was suspected and that their incidence would be appreciably increased if tissue were regularly submitted for histologic study. It was possible that the cases of so-called basal cell epithelioma arising on the basis of a mole or pigmented nevus belonged in this category.

CASE 9.—H. S., a woman aged 42, presented on her right temple what appeared to be an ordinary small pigmented mole, with fine hairs. It had been present for many years. The point of interest, however, was a split pea-sized smooth yellowish growth situated on the dorsum of the nose. The surface showed some fine telangiectases. The lesion had never bled and had undergone a gradual increase in size in the past year. The original growth at this site had been present for nine years, when in October 1933 it was removed by electrolysis. At that time it was regarded as of the same nature as the one on the right temple ("common mole"). After the removal, there was a gradual recurrence, more marked in the past year. In order to ascertain the nature of this recurrence, the lesion was excised in August 1937. At the end of two weeks the area had healed completely.

On histologic examination the epidermis was found to be approximately normal, with a few isolated hyperkeratotic accumulations in what appeared to be the openings of hair follicles or sebaceous glands. The growth was composed chiefly of large numbers of hypertrophied sebaceous glands. There were also numerous sweat glands. A moderate infiltration of round cells was observed about some of the blood vessels in the subpapillary layer, and the papillary zone revealed a few dilated capillaries. There were no nevus cells. The pathologic diagnosis was hypertrophied sebaceous glands, possibly a sebaceous adenoma.

From the nature of the microscopic anatomy, considerable doubt must be placed on the original diagnosis of mole in the sense in which that growth has been defined in this paper. The nature of the pathologic process probably explained the recurrence, for the major part of the growth was lodged deep in the cutis and its removal could not have been accomplished without some degree of scarring. In what seemed to be a case of recurrent mole, it was thought advisable to remove the growth in toto in order to establish the diagnosis and also to rule out any malignant change. This case illustrated another, perhaps not infrequent, possible clinical error in diagnosis of the common mole.

CASE 10.—M. M., a girl aged 17, presented a smooth dark brown nonhairy elevated nodule, measuring 7 mm. by 1 cm., on the left side of the forehead about 2.5 cm. from the hair line. The duration was said to have been between four and six months. The lesion on the forehead had been traumatized by the patient, with a resultant increase in its size. A portion of the lesion on the forehead was removed for microscopic examination, and after the receipt of the pathologic report, complete excision was advised. In addition to the lesion on the forehead, the patient presented other smaller and flatter pigmented marks on the left cheek, chin and chest which were said to have been present since birth. None of these seemed to show any evidence of activity.

The histologic section showed an epidermis that was fairly normal, with pigment in the basal epidermis, free in the upper part of the cutis and in the neoplasm cells. There were no mitotic figures, but there were many multinucleated cells. True clear cells were no longer present in abundance, there being only a few in the basal zone. Cellular elements in the cutis proper were variously sized and

shaped, some round, some polygonal and some spindle shaped; they contained large vesicular nuclei; a number were multinucleated; some were very small and some were infiltrating between bundles of connective tissue. Scattered throughout the entire cutis were large hyperchromatic cells, some isolated and some in strands and whorls. In the papillary zone there was considerable disintegration of cell bodies in the majority of the cells. Pigment was present in the upper part of the corium and in the papillary bodies. There were a few telangiectases. Segmentation with the formation of *thèques* was profuse throughout the section.

Fig. 12 (case 10).—Junction type nevus.

This condition must be looked on as a proliferating and infiltrating stage of a nevus of the junction type.

Case 11.—M. R., a girl aged 14, presented an area made up of many small roughly triangular and flat smooth pigmented nonhairy macules on the right lateral aspect of the chin, which had been present since birth. The area extended from the right side of the lower lip down to the upper part of the neck near the lower angle of the inferior maxilla. There was a pea-sized lesion, brownish in the center, with slight reddish tint at the periphery; at times it seemed more reddish, resembling an angioma; at other times it had a definite brown hue, as seen in an ordinary mole. The growth, which was smooth and slightly elevated, was removed for microscopic examination.

The section showed evidence of nevocarcinoma. Extending from the bottom of the section up to the epidermis was a dense epithelial cellular infiltrate. In the lower border of the epidermis there were groups and nests of cells similar to those in the cutis. The latter were not closely packed and had large hyperchromatic nuclei and definite bodies, and in places outlines of the cells could be seen which in some areas were multinucleated. In this area also there was a large amount of pigment. In the middle and deep portions of the cutis the cells were closely packed and took on spindle shapes.

The sections were submitted to Drs. Ewing and Fraser, who agreed that they showed no malignant change and that the condition was a neurofibroma with surrounding nevus, benign in character. Dr. Ewing expressed the opinion that the lesion should be treated with radium. Other sections were examined by Dr. S. W. Becker, of Chicago, who made the following report.

The section showed characteristics midway between those of a benign melanoma, or, in other words, a pigmented nevus, and a definitely malignant tumor. The deeper portions of the section gave no hint of malignant degeneration and were probably benign. The fact that pigmentation was limited to the superficial

Fig. 13 (case 11).—Junction type nevus? Pigmented patch of Recklinghausen's disease?

portion also was in favor of a benign condition. The groups of cells just beneath the epidermis situated in vacuole-like spaces were similar to those found in malignant neoplasms. They were not grouped together in masses, as in ordinary pigmented nevi, but were rather arranged at the periphery of the vacuole-like spaces, with the cellular process extending to the center and through the space. From the histologic picture, one surmised that the cells in the superficial portion were not entirely quiescent. Dr. Becker doubted, however, that a definite diagnosis of malignant melanoma could be made. He stated that, owing to the fact that the tumor was not a strictly quiescent nevus, it certainly would be advisable to treat it a "little more radically" than would be necessary for a quiescent lesion. Dr. Satenstein diagnosed the growth as a nevocarcinoma. Clinically, we felt this lesion was definitely benign, and in the two to three years that we have followed this patient, nothing has occurred to change this view.

CASE 12.—H. B., a man aged 23, had a growth on the flexor surface of the left forearm which had originated about six years ago. The mark, which was roughly circular in outline, measured about 1.5 by 2.5 cm. Its surface was irregular, smooth and devoid of hairs. There was a narrow peripheral ring which was light brown, while the central portion was dark brown, with two relatively

firm elevated areas surrounded by a zone that was slightly less pigmented. The patient stated that there had been no increase in size during the past two or three years, but he believed that the central papules had fused somewhat during that period. The lesion was excised widely and closed with dermal sutures. There was a pea-sized smooth brown lesion on the upper part of the left arm, of unknown duration. This lesion was also removed. On microscopic examination the lesion of the forearm showed an epidermis with decidedly irregular rete pegs and pigment both in the epidermis and in the upper part of the corium. There were strands of hyperchromatic epidermal cells. The changes were typical of the junction type nevus. The second section taken from the arm showed an epidermis with

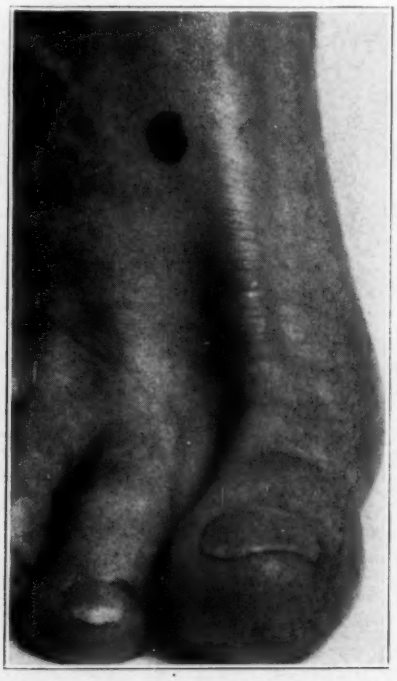

Fig. 14 (case 13).—Junction type nevus before removal.

irregular projections and infiltrating nevus cells in the corium and a slight amount of pigment. The diagnosis was intradermal nevus.

CASE 13.—S. M., a man aged 19, stated that the growth on the dorsum of the right foot had not appeared until two months before the present observation. The lesion measured 8 by 12 cm. and was smooth, slightly elevated, uniformly deep, brownish black and devoid of hairs. It had appeared suddenly. There was no history of trauma to that area or of a previous spot at the site. By means of the cutting current, the lesion was removed widely (fig. 14) with a 2 cm. border of normal skin. The wound healed completely without skin grafting.

Microscopic examination (fig. 15) of many sections showed that the entire growth had been removed and that a great deal of apparently normal tissue had

been included. The lesion appeared to be well localized chiefly in the lower epidermis and the immediately adjacent cutis. A large amount of pigment was observed in these areas as well as some in the upper portion of the epidermis, including the corneous layer. The major portion of the growth was composed of groups of cells (segregation) within *thèques* in the lower part of the epidermis. The cells showed nuclei of various shapes, with large conspicuous nucleoli and well developed particles of chromatin. The protoplasmic outlines were difficult to

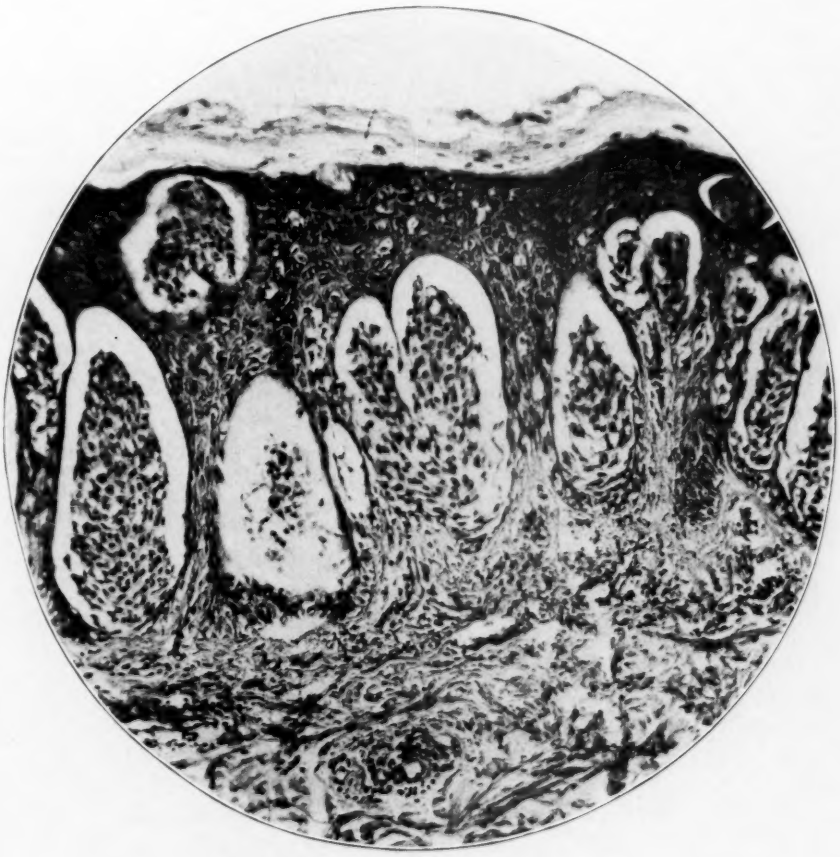

Fig. 15 (case 13).—Junction type nevus.

distinguish owing to the paleness of the cytoplasm. There were some large cells containing two nuclei and cytoplasm staining a deeper pink. Many cells showed pigment, usually in the form of fine granules and sometimes in larger granules, but on the whole these deposits were fairly uniform in size. Similar groups of cells were found just beneath the corneous layer, giving the impression that they were just about to be cast off. In the papillary and subpapillary layers were larger cells of various sizes which contained rather large granules of pigment of fairly uniform size and obscured the outlines of the protoplasm. However, it

appeared that the cells were disposed in sheets. In the nearby surrounding tissue in the corium, there was an inflammatory reaction in the form of several blood vessels surrounded by lymphocytes and a few plasma cells. There were no mitotic figures. The pigment was bleached by means of potassium permanganate and oxalic acid.

The diagnosis was junction nevus. The segregation with the development of *thèques,* which was one of the principal changes in this case, taken together with the other observations already enumerated, makes this type appear to be a rather dangerous lesion. Clinically, but for its unfavorable location and its smooth character devoid of hairs it did not look like a malignant growth.

Case 14.—H. B., a woman aged 33, had an irregularly shaped dark brownish black slightly elevated mark, the surface of which was uneven but not warty, just anterior to the right ear and at the lower border of the hair margin. The color of the lesion was uneven, being brownish with some darker black portions. The mark measured ½ by ¾ inches (1.3 by 1.9 cm.). There were numerous coarse black hairs, but it was difficult to determine whether they were peculiar to the nevus or whether the mark simply happened to be in a location where hair was normally present. There was a tiny ulceration in the center of the lesion that had bled. The patient was uncertain as to the exact duration but was certain that it had grown considerably in the past year or two. The lesion was excised, and the microscopic examination proved it to be a typical nevus of the junction type.

Case 15.—A. M., a woman aged 22, was born with a nevus on her right cheek near the angle of the jaw. It was an irregularly lobulated oval brownish lesion about 2 cm. in its longest diameter. The central portion was light brown, while a narrow periphery was darker brown. In the center, also, there was a small irregular fleshy brown raised area. The growth revealed many stiff hairs; some of these had been clipped by the patient, but none had been plucked. There had apparently been no increase in size from birth, nor had the lesion ever bled as a result of trauma. With the aid of local anesthesia the lesion was excised; complete healing occurred within a month.

Microscopic study showed the raised portion of the lesion to be composed of nevus cells in typical configurations, accompanied by thinning of the epidermis in the usual fashion. At the periphery of the section the epidermal layers showed a moderate degree of proliferation, which was considered normal by Dr. E. A. Barthel and evidence of the junction type change by Dr. Satenstein. Many hair follicles were observed throughout the section. The flat portion of the lesion showed essentially the same alterations except that the epithelial proliferation seemed to be composed chiefly of what might be called clear cells. The diagnosis was intradermal nevus in combination with the junction type.

Case 16.—A. M., a woman aged 45, presented a growth on the right side of her back which she stated was of six months' duration. The back and shoulders were covered with many freckle-sized pigmentary macules. The growth in question appeared to arise from the upper pole of a relatively flat smooth light brown pigmented area about 1 cm. in diameter. It was a shiny smooth black mass measuring 1.5 by 0.5 cm. There were no hairs. It had increased rather rapidly in size, and the patient mentioned that she thought it had developed from a freckle (lentigo maligna).

Fig. 16 (case 14).—Junction type nevus.

Fig. 17 (case 14).—Low power section of junction type nevus.

Fig. 18 (case 15).—Intradermal nevus in combination with junction type nevus.

Fig. 19 (case 15).—Low power section of intradermal nevus in combination with junction type nevus.

Microscopic examination showed that the epidermis was thinned and flattened. A large mass lined at the sides by epidermis dipped down as far as the middle part of the cutis and enclosed a group of cells of various size, some containing two or more nuclei. The cells had distinct bodies, and some also had distinct outlines. Some of the nuclei were large, and there was a fair number of mitotic figures. The vessels around the mass were considerably dilated, and around them there was a moderate amount of focal cellular infiltration. Moreover, there was an intense diffuse cell infiltration, with many small thin-walled vessels. It consisted mainly of small round cells, a few plasma cells and connective tissue cells, some with pigment. The mass in areas reached within the basal zone of the epidermis. The diagnosis was a nevus of the typical junction type.

CASE 17.—H. A., a woman aged 42, had a smooth pea-sized slate blue lesion on the dorsum of the left hand, which had been present at birth or had appeared shortly after. The color was uneven; the peripheral blue was darker than that

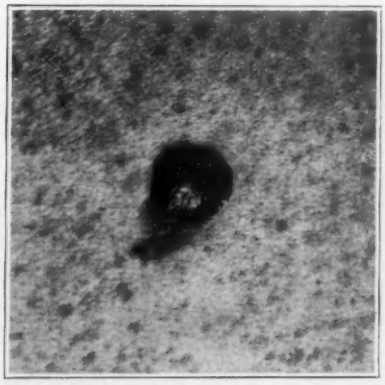

Fig. 20 (case 16).—Junction type nevus.

in the center. There had been no bleeding and no increase in size. The growth was removed by wide excision.

Histologic examination (fig. 22) showed an epidermis that was apparently unchanged. There were many cells of the *cellule claire* type in the basal layer. In the middle two thirds of the cutis there were numerous stellate cells containing pigment in the form of coarse granules that seemed to be nearly uniform in size and shape. In this area of pigmentation the collagen bundles seemed undisturbed except that there was a proliferation of spindle-shaped fibroblastic nuclei. In this zone also the pigment was distributed especially densely about the sweat glands, possibly in relation to the blood supply about these structures. The distribution about the vessels was also noted in the papillary bodies, where, however, there was much less pigment and that present appeared to be restricted to the parts directly adjacent to the capillary walls. There were some deposits of pigment that seemed to lie freely in the interstitial tissues, but this impression was probably caused by cross sections through the cytoplasm of the connective tissue cells. The distribution of the pigment appeared to explain the lack of uniformity in the color of the lesion, creating what has been called a speckled appearance. The diagnosis was blue nevus.

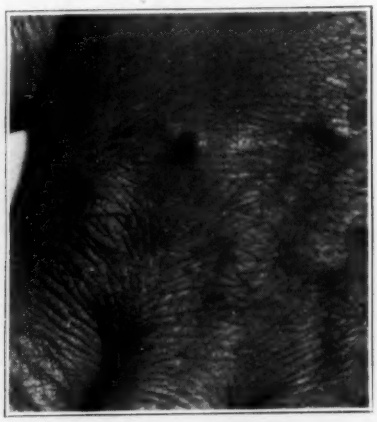

Fig. 21 (case 17).—Blue nevus.

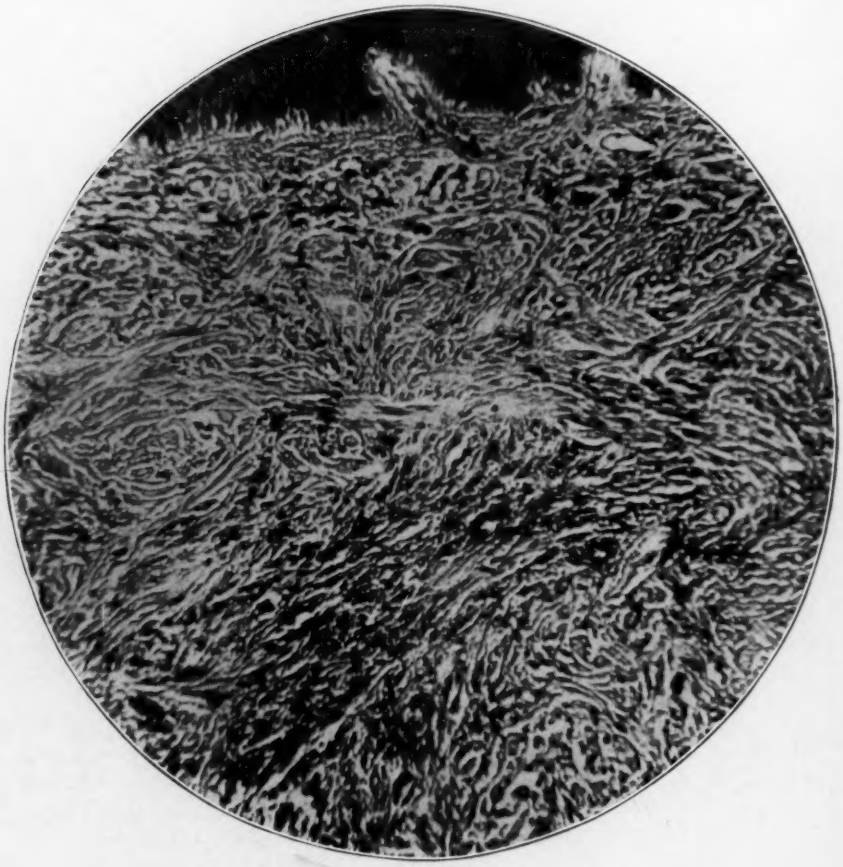

Fig. 22 (case 17).—Blue nevus.

From birth, also, there had been present a pea-sized relatively smooth moderately firm skin-colored lesion on the right cheek near the nose; the growth showed a definite brownish tone, particularly in the center, with a few telangiectatic vessels. There were some delicate hairs. There had been no bleeding or evident increase in size. The entire growth, together with the surrounding normal skin, was excised and on histologic examination proved to be a typical intradermal nevus.

SUMMARY AND CONCLUSIONS

The need to establish a simplified uniform nomenclature, so that each term used has a specific, universally recognized meaning, is of paramount importance. An outline is submitted to assist in the classification of pigmented nevi and moles from both the clinical and the histologic standpoint.

The relation of the various marks to cancer is clearly defined, and illustrative case records and photographs are included.

Reasons are given for restricting the designation "common mole" to that type of lesion characterized histologically by intradermal collections of nevus cells. We find no evidence that the "common mole" (the pure form, not combination types) ever develops into cancer.

Malignant melanomas apparently have their origin in nevi of the junction type, which are clinically characterized as smooth nonhairy pigmented spots.

The blue nevus appears to be a benign lesion and should not be confused with the dangerous slate black or blue-black melanoma.

ABSTRACT OF DISCUSSION

Dr. Fred Wise, New York: I once had occasion to treat a brown hairy mole in the clinic while Dr. Bruno Bloch stood by. As I was about to apply the solid carbon dioxide pencil, Dr. Bloch grabbed my arm and said, "Don't do that!" I said, "Why not?" He replied, "Because you are liable to cause a malignant growth." To my question whether he had ever encountered malignant changes subsequent to the treatment of brown hairy moles, he replied that he had seen several of them. In my own experience no such thing has occurred. You will recall the photograph on the screen, demonstrated by Dr. Traub, of a pale, flat, pigmented nevus on the left side of the chin of a young girl. She was originally under my observation at the clinic of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital. I advised treatment with solid carbon dioxide, because I could determine by clinical observation that the mole was a simple pigmented nevus of the smooth and pale variety. Subsequent events proved this to be the correct diagnosis. A small section of the mole was examined microscopically; the histologic description, however, included the term "malignancy," much to my astonishment. In many instances of this type the clinical diagnosis seems to have more weight than the microscopic; Dr. Traub's case is a good example.

Dr. Ruben Nomland, Chicago: How does Dr. Traub explain the so-called implantation melanoma of the sole? I have observed several cases in which a dark spot developed on the sole after prolonged irritation (usually by a nail in

the shoe) and then after a variable period, five to twenty years, a malignant melanoma developed. What is the explanation of such a finding?

I should also like to question Dr. Traub concerning the treatment of such lesions and to ask him how he explains the development in senile persons of pigmented lesions with extremely dark pigment, which occasionally undergo malignant change.

Dr. J. Gardner Hopkins, New York: When I answered Dr. Traub's questionnaire I had to say that I have never observed the development of malignant change in a mole which I had previously observed in an apparently benign stage. However, physicians must all have seen malignant melanomas which the patient stated had originated from an ordinary mole.

Dr. Traub brings up the fundamental question whether supposed moles which develop into lethal metastasizing tumors are identical with the innumerable moles which remain harmless or whether they have special malignant potentialities from the beginning. I wish he would explain further how he differentiates the two groups, either in clinical or in histologic terms.

Dr. George M. MacKee, New York: Dr. Traub's paper is really a preliminary report. He is endeavoring to find a way to determine on clinical grounds the danger associated with the different varieties of nevi. He has made some headway, but he has an enormous amount of work ahead of him. What dermatologists are trying to do is to classify moles and nevi clinically, largely for the sake of convenience, study the clinical appearance and behavior, agree on the clinical diagnosis and then verify or refute the clinical diagnosis histologically. It has been interesting work. Often, indeed, the clinical diagnosis is erroneous, but as a result of this experience one is clinically correct more often than formerly. One hears the terms common mole and blue-black mole; also, there is a difference of opinion as to the potential danger inherent in the different moles. It is hoped that eventually it will be possible to classify moles clinically, give them convenient names, estimate the degree of potential danger and outline therapy in relation to these facts. One realizes, of course, that histologically there is no precancerosis, but certainly some moles are more likely to become malignant than are others. It is important to be able to differentiate clinically between benign and malignant moles and to estimate the potentialities of benign moles. Dr. Traub has had some success. I hope that he will continue with this difficult task and have further success.

Dr. Nelson P. Anderson, Los Angeles: Physicians are all familiar with the ordinary brown pigmentation that occurs in the vicinity of some melanomas that are actually malignant. I believe that so-called brown moles which have become malignant are moles which have originated from a minute group of nevus cells and that the characteristic brown pigmentation about them is that of a nevus or melanoma which has already undergone malignant change. This possibly explains in some instances the patient's statement that he had a simple brown mole in the affected area.

Dr. Fred D. Weidman, Philadelphia: If there is any one kind of lesion that comes with greater frequency than another through a laboratory, it is the mole, and opinion ought to be well crystallized by now; yet it is not. I should like particularly to get further information from Dr. Traub as to the differentiation the authors make between the true blue nevus and the other blue mole of the epidermis, which may be their "junction lesion" as I understand it. According to Jadassohn, the blueness depends on the depth of the pigment; this seems to be generally accepted, but I do not know that it is absolutely proved. In any event,

the pigment in an epidermal nevus may lie just as deep as the pigment in a blue nevus, and the lesion could be rated clinically as blue-black nevus. Incidentally, at a recent conference the registry committee of this association disagreed as to the likelihood of malignant change developing in the blue nevus. Dr. Satenstein said that he had never seen it.

One should not attempt to classify a congenital lesion, such as a nevus, as malignant or nonmalignant on purely statistical grounds; that is, on the basis of its location in the epidermis, at the junction point or in the corium. I think that can be done only after the accumulation of ample statistics and after analysis and resolution of the data. I doubt that any such analysis has been made. Until it has been made, I feel that it is necessary to decide whether a lesion is malignant or not on histologic criteria which general pathologists have known for years. In the final analysis there are two such criteria. The first is evidence of some cellular change indicating an alteration in the direction of malignancy. McCarthy's "one-eyed cells" are in point here; they have been described in contributions from the Mayo Clinic, where pathologists feel that they can identify an individual cell as genuinely cancerous. Only the trained pathologist is qualified to attempt this.

The second criterion of malignancy is permeation and invasion of tissue. If it can be determined that certain nevus cells are extending beyond the usual realm of ordinary nevus cells, say into the level of the sweat glands, the process is malignant. Until there are ample, complete and convincing statistics on data such as those reported today, physicians should depend on these two items. One must remember that the nevus does not follow accurately the rules for normal epithelium, because it is a congenital anomaly. That being the case, the epithelium must be expected to be found in positions deep in the lymphatic spaces, positions which the general pathologist will say are abnormal for epithelial cells; ergo, cancer. Consequently, the general pathologist commonly and erroneously diagnoses benign nevi as cancerous. It is only after the general pathologist has had some experience along these lines that he learns his lesson. Fortunately, the American Association of Pathologists and Bacteriologists has selected the pathology of the skin as its main theme for discussion this year. Dr. Lee McCarthy is the dermatologic consultant, and general pathologists will be advised in this most important matter.

Dr. Eugene F. Traub, New York: In the case of the flat, smooth, pigmented, nonhairy nevus on the young girl's chin, we simply removed a specimen to add to our collection, never for a moment believing that there might be a question of malignancy. Nevertheless, two New York pathologists independently called the lesion a malignant melanoma, while a third thought it might be one of the pigment spots of von Recklinghausen's disease. Dr. Becker of Chicago also had an opportunity to study this slide, and he was doubtful as to whether the process was benign or malignant. A great difference of opinion, therefore, is possible after examination of sections from such lesions, just as it is when the patient is studied solely from a clinical standpoint. The classification just submitted unquestionably is far from perfect and must be subject to revision and correction, but it seems to me that even an imperfect classification which can be revised as additional information is forthcoming is better than none. It may at least help to simplify the terminology, a distinct advance in itself.

There is considerable difference of opinion as to the actual importance of trauma, especially with some of these growths, and there are other factors, naturally, as Dr. Weidman pointed out, which help to determine whether or not the lesion is going to be cancerous. I feel that many lesions which are assumed to have originated from nevi are malignant from the onset and have had no

relation to any type of nevus, even though some sort of mark may have been present for many years. I refer particularly to the type of mark that might have been assumed to be a nevus rather than a "senile freckle" or premalignant spot of the sort seen in aged persons. It is an accepted fact that not all malignant melanomas originate from nevi. While the majority of authors state that a rather high percentage of malignant melanomas do so originate, it is probable that more careful investigation of histories and further study may prove the estimate rather high. That is another reason why one should be careful about terminology in describing the original mark, so that future authors collecting such statistics will not confuse the issue. It is often a mistake to accept a patient's unsupported account of the presence or absence of a preexisting mole on which malignancy has developed.

To answer the question about implantation of melanomas, I refer you to the recent work by Peer and Paddock. While this question is still in dispute and cannot be finally settled at this time, Peer and Paddock, who buried full thickness skin grafts and other skin grafts from which the epidermis had been shaved off and subsequently removed these areas for microscopic study, showed what might be expected to happen to implanted particles of skin. They found that in a comparatively short time all portions of the epidermis and the cutis, even including the hair follicles and hairs (but with the exception of the sweat glands in some instances), were absorbed and had disappeared. Therefore, probably any epidermal structure that might be carried in by an instrument or nail puncture is absorbed before it can start a new growth. Of course, a puncture wound may, without carrying cells down into the deeper tissues, give rise to a melanoma in some other way, perhaps by direct injury to some of the pigment-forming cells themselves.

Concerning Dr. Weidman's question about the blue nevus, one must again admit to a difference of opinion. Satenstein, Becker and others who have had a wide experience in examining such sections have never seen a malignant growth result from such a lesion. In our series we have not seen a blue nevus become malignant. It is possible that in cases in which a malignant melanoma developed the original lesion was not a blue nevus but some other pigmented mark clinically resembling it. There are a number of marks which clinically resemble the blue nevus, so that in some instances a histologic examination is necessary before the diagnosis can be definitely established. In cases in which malignant change has been described as developing in a blue nevus, the growth has been a melanosarcoma. No doubt some of the slate black moles which are junction nevi and potentially malignant melanomas and which differ widely histologically from the blue nevus are the lesions that cause the confusion.

The type of lesion that I believe to be innocent is the hairy pigmented nevus. When hair is an essential part of the nevus, regardless of the color, in most instances the lesion remains benign. The warty lesions are also, in our opinion, unlikely forerunners of malignant melanoma. It is the smooth, flat, pigmented, nonhairy and nonwarty lesion that is most dangerous. The color apparently is not of great importance.

LXXXIII.—MALASSEZIA FURFUR, THE CAUSE OF TINEA VERSICOLOR

CULTIVATION OF THE ORGANISM AND EXPERIMENTAL PRODUCTION OF THE DISEASE

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The cultivation of Malassezia furfur, the fungus responsible for the disease pityriasis (tinea) versicolor, has been seldom accomplished, in spite of the large number of cells of the organism in the stratum corneum of the epidermis. After making several unsuccessful attempts, I finally cultured it and reported my work in a previous paper.[1]

It is the purpose of this communication to review briefly the characteristics of the organism in tissue and in culture and to give further data as to the experimental inoculation of the fungus into laboratory animals, human volunteers and the chorioallantoic membrane of the developing chick.

HISTORICAL REVIEW

Tinea versicolor was first recognized and demonstrated as a fungous infection by Eichstedt.[2] In 1864 Köbner [3] claimed to have transferred the fungus to his own skin and to that of rabbits. Hallier [4] observed the growth of an organism which he first classified as an Aspergillus and then as a Stemphylium. Neumann [5] observed the formation of

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Studies, observations and reports from the Laboratory for Mycology and Dermatological Research of the Barnard Free Skin and Cancer Hospital, service of Dr. M. F. Engman Sr.

1. Moore, M.: Cultivation of Malassezia Furfur, Etiological Agent of Pityriasis (Tinea) Versicolor, Mycopathologia **1**:53, 1938.

2. Eichstedt, E.: Ueber die Krätzmilben das Menschen, ihre Entwicklung und ihr Verhältniss zur Krätze, Notiz. a. d. Geb. d. Natur- u. Heilk. **38**:105, 1846.

3. Köbner, H.: Klinische und experimentelle Mittheilungen aus der Dermatologie und Syphilidologie, Erlangen, F. Enke, 1864, p. 41.

4. Hallier, E.: Die pflanzlichen Parasiten des menschlichen Körpers, Leipzig, Wilhelm Engelmann, 1866, p. 79.

5. Neumann, I.: Textbook of Skin Diseases, translated from the second German edition by A. Pullar, London, R. Hardwicke, 1871, p. 322.

daughter cells of the fungus into tubular structures but did not isolate the microbe. Von Sehlen [6] and Unna cultured an organism which was septate and branched at the ends, liquefied gelatin and became brown in culture. Kotljar [7] isolated a fungus from scales with which he produced brown spots on a dog. His microbe was named Oidium subtile, but it appeared to be a possible species of Actinomyces. Spietschka [8] used sterilized urine in his mediums and obtained a slowly growing fungus in 12 instances. He inoculated 6 human volunteers and himself, with negative results in all but a 22 year old patient with lupus who showed browning after nine days.

Matzenauer [9] used various sugar mediums and was able to isolate two colonies on Finger's "epidermin agar" from several hundred poured plates. To this author should be given the credit for having successfully cultivated M. furfur. He inoculated himself with this fungus and noted a lesion three months later. Gastou and Nicolau [10] confirmed Matzenauer's work, using placental extract in their medium. They cultured the organism on three occasions.

Little work had been done since these reports until 1923, when Schmitter [11] isolated an organism which suggested a bacterial contamination. Nine years later Kambayashi [12] reported the growth of a fungus nine months after inoculation. The length of time necessary for the development of the microbe and its growth near the rim of the plate suggested a contamination. In 1937 Marquardt [13] used Grütz's medium [14] and obtained growth in five of eleven attempts. His inoculations in guinea pigs and human beings gave negative results.

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6. von Sehlen: Ueber die Zuchtung von Pityriasis versicolor, Tagebl. d. Versamml. deutsch. Naturf. u. Aerzte, 1880, p. 600.

7. Kotljar, E. J.: Morphologie des Mikrosporon furfur, Vrach, 1892, no. 42, p. 1055; no. 43, p. 1083; abstracted, Arch. f. Dermat. u. Syph. **26**:312, 1894.

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9. Matzenauer, R.: Zur Bacteriologie der Pityriasis versicolor, Arch. f. Dermat. u. Syph. **56**:163, 1901.

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11. Schmitter, F.: The Aetiological Fungi of Tinea Versicolor and Tinea Flava, J. Trop. Med. **26**:190, 1923.

12. Kambayashi, T.: Eine botanische Untersuchung des Microsporon furfur Robin, Botan. Mag., Tokyo **46**:232, 1932.

13. Marquardt, F.: Die Kultur des Mikrosporon furfur, Dermat. Wchnschr. **104**:177, 1937.

14. This medium consists of 9 Gm. of agar, 2.5 Gm. of peptone, 2.5 Gm. of sodium chloride, 2.5 cc. of glycerin and 30 Gm. of "nervina malt" in 500 cc. of distilled water.

EXPERIMENTAL CULTURING

The cultivation of Malassezia furfur was successful in a broth medium (peptone, 1 per cent, and maltose, 4 per cent) after several years of attempts with various routine laboratory agar mediums.

The lesions were cleansed with 70 per cent alcohol; scrapings were made with a sterile scalpel, and the cleansed scales were transplanted directly into tubes of the broth. M. furfur was grown on two occasions from the scales of 9 patients chosen at random when the cultures were incubated at 37 C. There was no growth in the tubes exposed to room temperature. The scales for both cultures were obtained from early, actively spreading lesions.

The cultures grew as small islets on the surface of the broth and as a sediment at the base of the tube. Subcultures from both growths and from the shaken-up growths always resulted in similar cultures.

DESCRIPTION OF THE FUNGUS

In young lesions M. furfur appears as a fine filamentous, branching mycelium, 1.5 to 2 microns in diameter (fig. 1, *1*). As the lesions become older, the fungus forms cross walls and short hyphal cells, 1.5 to 4 microns in diameter and 10 to 16 microns the length of the axis. These cells in turn become spherical free arthrosporous cells, vary from 3 to 8 microns in diameter, and are observed associated with the filaments in old lesions (fig. 1, *2*).

On artificial mediums when first grown the organism manifests itself as spherical budding cells at the base of the tube and as germinating fusiform-like cells at the surface. The latter cells produce cross walls, become elongated and branch. In subcultures of the growths colonies develop on various mediums which are flat and dull or moist, mucoid and shiny, verrucous, cerebriform to rugose, vermiculate and somewhat velvety; on wort agar in particular there develops an arborescent growth (fig. 2). The color of the cultures varies in different mediums from whitish gray and fawn to creamy buff and light cinnamon in young cultures to ochraceous buff and dark cinnamon in older cultures. The colors seem to correspond to those observed in the lesions of human beings. As the growths of the fungus become old the organism loses its pigment.

Microscopically, the fungus in culture shows a characteristic development, which begins with the formation of a somewhat fusiform cell approximately 3 by 16 microns, with convolutions and budlike projections at each end. As the cells increase in size they form a cross wall, become elongated, eventually produce more transverse septums and then branch. The hyphae measure approximately 1.5 to 5 microns in diameter. The filaments become beaded to form oidioid structures,

which are walled off and arthrospore-like and then spherical, ellipsoid or ovoid and thick walled, simulating the blastospores seen in scales of the infection. These cells measure approximately 4 to 10 microns in diameter, depending on the medium on which they are grown.

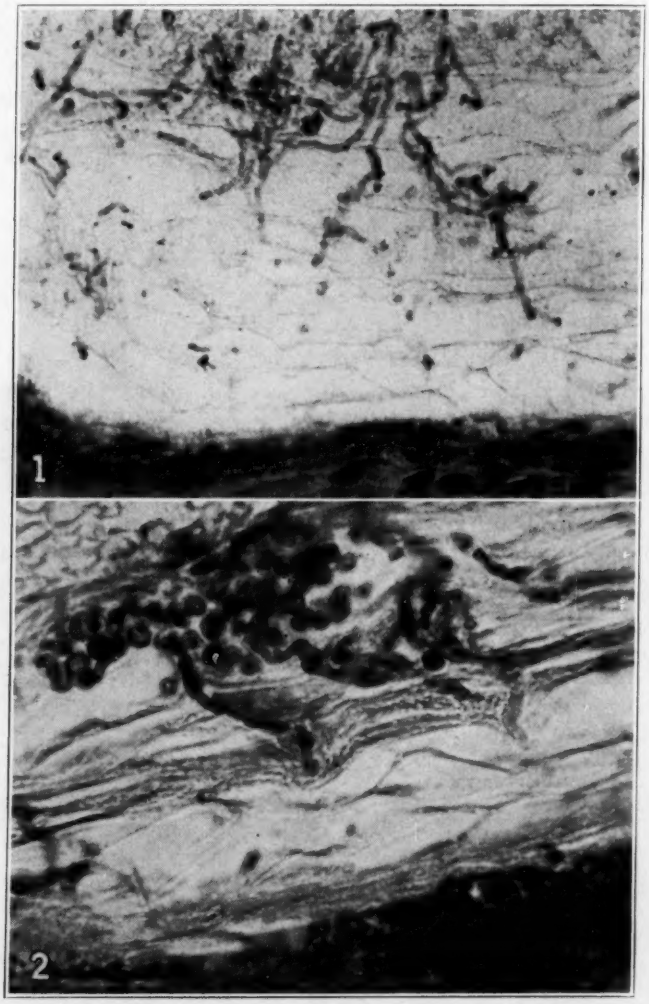

Fig. 1.—Malassezia furfur in lesions: (1) biopsy section (low power) showing young filaments (methylene blue and eosin) and (2) histologic section showing spherical cells and filaments in older lesion (methylene blue and eosin, with oil immersion).

The fungus also produces chains of thick-walled, sclerotic cells, with fine nonseptate, dendritic and intertwining hyphae. Asci and ascospores

have not been observed in either old or young colonies or on favorable or unfavorable mediums.

On biochemical study M. furfur liquefied gelatin beginning on the fifth day at the surface. Litmus milk was acidified after ten days but showed no curdling. Acid was produced, but no gas, with dextrose, d-oxylose, amygdalin and d-levulose. Neither acid nor gas was produced with maltose, rhamnose, raffinose, dextrin, d-mannitol, l-arabinose and starch.

EXPERIMENTAL INOCULATIONS

The ultimate proof of the etiologic significance of a fungus naturally rests with its ability to reproduce the disease for which it is held responsible. The inoculation of rabbits, guinea pigs, rats and mice gave negative results, both by the percutaneous method and by the direct

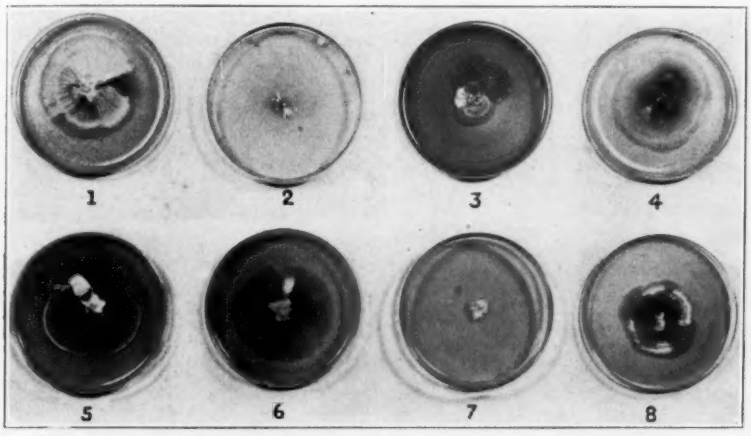

Fig. 2.—Agar cultures of Malassezia furfur: (1) Czapek's, (2) corn meal, (3) wort, (4) Sabouraud's maltose, (5) Sabouraud's dextrose, (6) potato-dextrose, (7) nutrient and (8) glycerin.

application of fungi to the intact skin. In rabbits and guinea pigs inoculated intracutaneously or intratesticularly granulomatous lesions developed which were hard, heavily infiltrated and erythematous and showed microscopically a heavy eosinophilic infiltrate.

Inoculations of the human skin (percutaneously or intact) gave favorable results in 3 of 8 volunteers. The reaction at the site of inoculation in 2 of the volunteers appeared as a follicular outgrowth, while a typical lesion, starting in approximately two weeks, developed in the third person. Scrapings made from the site of inoculation in the third patient revealed the formation of spherical cells after the first week, with a complete conversion of the filaments into spherical cells after the third week. Scrapings made at weekly intervals revealed only

spherical cells for three weeks (fig. 3, *1*), but after the fourth week rod formation was apparent as a result of the germination of the cells. Examination of scrapings from the site of inoculation in the fifth week revealed spherical cells and formation of filaments (fig. 3, *2*). When

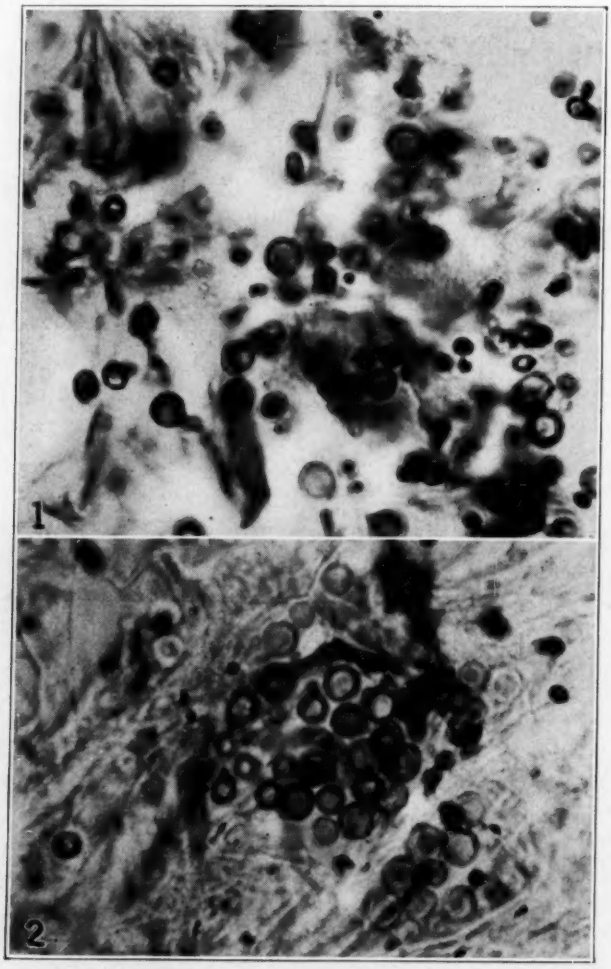

Fig. 3.—Malassezia furfur in experimental lesion: (1) spherical budding cells after three weeks (methylene blue and eosin, with oil immersion) and (2) spherical and germinating cells after five weeks (methylene blue and eosin, with oil immersion).

compared with the organism seen in scrapings from a spontaneous infection, the fungus observed in the experimental lesion after the fifth week presented similar morphologic structure and cellular measurements. M. furfur thus showed a reversion to its original parasitic state. The fungus grew profusely at the site of inoculation.

As a further method of determining the etiologic significance of the fungus isolated from lesions of pityriasis versicolor and identified as M. furfur, the microbe was transplanted directly onto the chorioallantoic membrane of the developing chick. The membranal reaction consisted

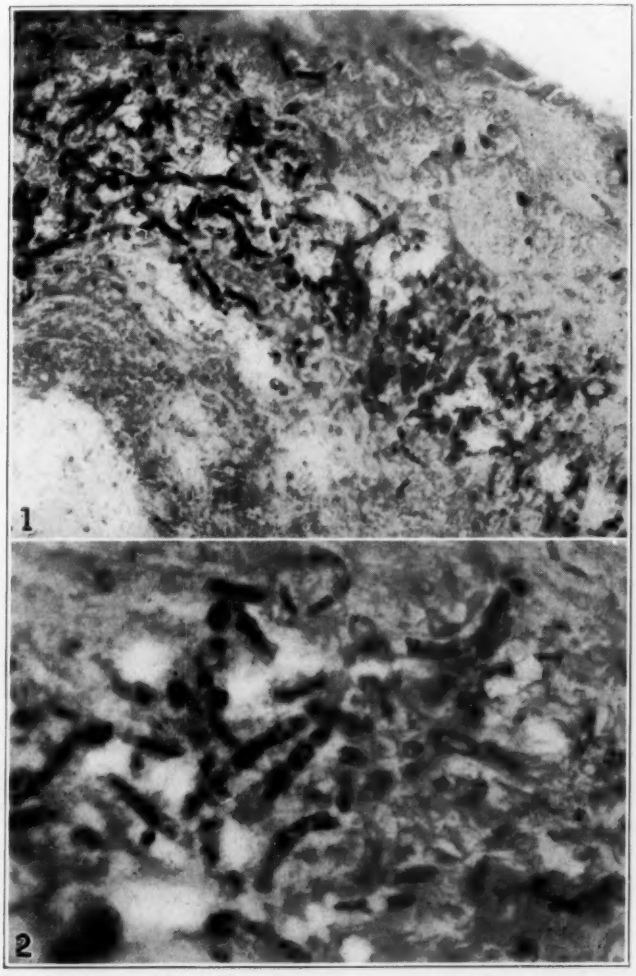

Fig. 4.—Photomicrographs of malassezia furfur: (1) in peripheral growth of inoculum on chorioallantoic membrane of developing chick (450 ×) and (2) on chorioallantoic membrane (877 ×).

in a nodular growth which microscopically showed a heavy infiltrate of monocytes at the junction of the fungous inoculum and the ectoderm. The ectoderm was stimulated to marked proliferation of ectodermal cells, which invaded the mesoderm. The mesodermal layer showed, in addition to islets of ectodermal cells, groups of leukocytes, fibroblasts and

apparently ectodermal pearl formation, an indication of hyperkeratinization. Of chief interest, however, was the well developed growth of M. furfur at the periphery of the inoculum, with the appearance of the characteristic spherical cells and filaments seen in scrapings from a human lesion (fig. 4).

SUMMARY

It is the purpose of this paper to emphasize again that Malassezia furfur, the cause of tinea versicolor, can be cultivated, as was first pointed out by Matzenauer in 1901, confirmed by Gastou and Nicolau in 1902 and further confirmed by me in 1938.

The presence of many different, harmless and cultivable fungi on the skin has complicated the true significance of the organism isolated by Matzenauer. The lack of conclusive evidence as to the pathogenicity of the numerous fungi isolated since Matzenauer's work and the adverse conditions of growth certainly help to rule out many of these organisms.

The fungus which is briefly described here was isolated on two occasions from 9 patients. It corresponds to the microbe described by Matzenauer and reproduces in culture the characteristics of M. furfur seen in scrapings from a spontaneous lesion. The organism in culture, however, shows varying cellular measurements, which is due to the constituents of the medium on which it is grown. The cultures vary widely in appearance, depending on the medium employed.

The fungus liquefied gelatin beginning on the fifth day. Litmus milk was acidified after ten days, without curdling. Acid was produced, but no gas, with dextrose, d-xylose, amygdalin and d-levulose. There was no acid or gas produced with maltose, lactose, saccharose, d-galactose, rhamnose, raffinose, dextrin, d-mannitol, l-arabinose or starch.

Experimental inoculations by the percutaneous method or by the application of the fungus to the intact skin of rabbits, guinea pigs, rats and mice gave negative results. Intracutaneous and intratesticular inoculations in rabbits and guinea pigs resulted in granulomatous lesions which were infiltrated, erythematous and hard. The inoculation of human volunteers either percutaneously or by the application of fungi to the intact skin gave favorable results in 3 of 8 volunteers. In 2 follicular outgrowths developed at the site of inoculation, while in 1 a typical lesion developed, starting in approximately two weeks. The organism grew profusely at the site of inoculation, first as a spherical budding cell for approximately three weeks; then, as a result of the germination of these cells, filaments and blastospore-like cells developed to simulate the microbe in its parasitic role. As a further check, the fungus was transplanted onto the chorioallantoic membrane of the developing chick, where it produced a reaction in the layers of this structure, with a reversion of the cells to the morphologic structure characteristically seen in scrapings from lesions of human beings.

LXXXVIII.—A SEARCH FOR FILTRABLE VIRUSES IN CUTANEOUS DISEASES OF UNKNOWN ETIOLOGY

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The present report deals primarily with the application of a recently developed experimental method to the etiologic problems of a group of cutaneous diseases the causes of which are unknown or in dispute. Most of the clinical material included in this study came from cases of psoriasis, pityriasis rosea and lichen planus. The experimental investigation of 7 cases of pemphigus vulgaris is the subject of a separate communication.[1]

The methods of mycology and bacteriology have been extensively employed in attempts to determine the causes of the previously mentioned cutaneous diseases, but to date their origin remains obscure. It was therefore determined to reinvestigate the conditions by means of the technic of egg inoculation which was developed by Goodpasture [2] and his co-workers for the study of filtrable viruses and other infectious agents. This method utilizes the embryonic chick and its enveloping membranes as an experimental animal. The advantages of the method are apparent from the fact that a great variety of pathogenic microorganisms have already been successfully cultivated in the chorioallantoic membrane of the developing chick. Numerous viruses, bacteria and fungi are included in the list. The freedom of the embryo from bacteria and other infectious agents, as well as from previous sensitizations, especially recommends the technic as an approach to etiologic problems in which microbic action or products may play a part. The embryo has a high degree of susceptibility, which is not shared by the adult of the species as regards the majority of the parasites that have been cultivated in the chick embryo. It was assumed, therefore, that if any of the dis-

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Studies, observations and reports from the Research Department and the Department of Dermatology, the Barnard Free Skin and Cancer Hospital, St. Louis, service of Dr. M. F. Engman Sr.

1. Markham, F. S., and Engman, M. F., Jr.: LXXXVI.—An Inquiry into the Cause of Pemphigus: Is It a Virus Disease? Arch. Dermat. & Syph. **41**:78 (Jan.) 1940.

2. Goodpasture, E. W.: Some Uses of the Chick Embryo for the Study of Infection and Immunity, Am. J. Hyg. **28**:111, 1938.

eases concerned in the present undertaking were of virus origin the developing egg might offer a suitable medium for their demonstration and study.

METHOD AND MATERIALS

Fertile eggs were incubated for nine to twelve days at 38 C., after which the chorioallantoic membrane was exposed by removing a small segment of the shell and shell membrane. After inoculation the opening was closed with a sterile cover glass and sealed with a mixture of petrolatum and paraffin. Inoculated eggs were incubated at 35 C. for four to ten days, during which time the membranes were observed for evidences of infection.

In so far as possible all patients selected for study had early active stages of disease. Biopsy specimens were finely minced with curved iris scissors and ground in a sterile mortar with powdered pyrex glass. The resulting pulp was taken up in 3 to 5 cc. of sterile saline solution or broth and allowed to stand until the gross particles settled out. The supernatant fluid was used for inoculations. Portions of 0.05 to 0.1 cc. of such preparations, whole blood, serum, spinal fluid or fluid from blisters, were usually inoculated onto the chorioallantoic membrane of each of three to six eggs.

Some specimens were taken from psoriatic lesions, after removal of the superficial scales, by clipping out small bits of epithelium, such as are used for skin grafts, with curved iris scissors. Two or three of these fragments were placed on the membrane of each of three or more eggs.

Specimens of skin were taken after light superficial sterilization with dilute tincture of iodine (approximately 0.1 per cent).

Tissues for histologic examination were fixed in Zenker's solution (prepared with acetic acid), embedded in paraffin and stained with hematoxylin and eosin or with eosin and methylene blue.

RESULTS

Pityriasis Rosea.—Specimens from 15 patients were examined. Biopsy material from 5 patients and blood from 10 others were inoculated onto egg membranes. Blood serum from 1 patient was injected in 0.03 cc. amounts intracerebrally in four white mice (Buffalo strain).

Although some of the specimens were carried through three to five serial transfers on the chorioallantoic membrane, no evidence of infection either gross or microscopic appeared in the inoculated chick tissues. All the mice remained symptomless during an observation period of six weeks.

Psoriasis.—Specimens from 19 patients were examined. Biopsy material from 6 patients, clippings of skin from 8 and blood serum from 3 others were inoculated onto the chorioallantoic membrane of developing eggs. Suspension of triturated scales and scrapings from psoriatic lesions of 2 patients were inoculated onto the scarified corneas of rabbits, one animal being used for each specimen.

Although some of the specimens were given three to six serial passages on the chick membrane, none of the inoculations resulted in

the appearance of lesions differing from those sometimes seen on inoculated or uninoculated control membranes. No vesiculation, keratitis or other manifestation of disease followed the corneal inoculation of the rabbits.

Lichen Planus.—Specimens from 11 patients with this disease were examined. Biopsy material from 6 patients, blood serum from 4 and spinal fluid from 2 were inoculated onto the chorioallantoic membranes of developing eggs.

Several of the specimens were subjected to serial passages on the egg membrane, in some instances as many as six times, but in no case did distinctive lesions either gross or microscopic appear on the inoculated membranes.

Other Diseases.—Spinal fluid from 1 and blood serum from 2 patients with lupus erythematosus, blister fluid from 1 with erythema bullosum, blood serum from 1 with erythema multiforme, whole blood from 1 with lymphatic leukemia and 1 with aplastic anemia, and biopsy specimens from 1 patient with mycosis fungoides and 1 with granuloma inguinale were inoculated onto the chorioallantoic membranes of developing eggs.

None of the materials gave rise to lesions on the inoculated egg membranes.

COMMENT

The susceptibility of embryonic tissues to infectious agents is well known. Not only are the young usually less resistant to a given parasite than the adults of the same species, but there are many instances in which the prenatal animal has been shown to be susceptible to infections to which the postnatal animal is completely resistant. It was therefore assumed that the chances of demonstrating unknown viruses or other infectious agents would be greatly increased by the use of the developing chick as an experimental animal for the study of cutaneous diseases. Moreover, since the embryonic chick lacks the normal microbic flora and fauna of the adult, the risk of encountering misleading spontaneous infections would be considerably lessened. Finally, the ectodermal origin of the exposed surface of the chorioallantoic membrane was thought to be an additional point in favor of the use of the embryonic chick in the experimental investigation of cutaneous diseases.

In spite of these advantages I was unable to detect the presence of filtrable viruses or other infectious agents in any of the specimens examined by this method. It should be pointed out, however, that the failure to demonstrate an infectious agent by the inoculation of experimental animals is not conclusive proof of noninfectious causation. Such cutaneous diseases as verruca vulgaris and herpes zoster have not been

reproduced successfully in laboratory animals. Nevertheless, reproduction of these diseases by the inoculation of human volunteers with filtrates, together with the characteristic cytologic changes in the lesions, argues strongly for their virus causation. With the possible exception of pityriasis rosea, this type of evidence is lacking in the cutaneous diseases studied in this investigation. On the basis of clinical, histologic and epidemiologic evidence, as well as the experimental data herewith reported, I am inclined to assume that the cutaneous diseases examined in the present study are of noninfectious origin.

PITYRIASIS ROSEA

REVIEW OF THE LITERATURE AND REPORT OF TWO HUNDRED AND NINETEEN CASES, IN THIRTY-EIGHT OF WHICH CONVALESCENT SERUM WAS USED

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I. INCIDENCE

Nékám [1] observed pityriasis rosea in 4 per cent of 100,000 cases of cutaneous disease, while Stelwagon,[2] in 123,746 cases collected by the American Dermatological Association from 1878 to 1887, found the disease in only 0.057 per cent. MacLeod [3] found 3 cases of pityriasis rosea per thousand cases of cutaneous diseases in children under 14 years of age observed at the Victoria Hospital. Graham Little [4] saw 6.7 cases per thousand in a dermatologic clinic for adults and children and 4.7 per thousand in a children's clinic. Benedek [5] quoted statistics from thirteen authors. The frequency of pityriasis rosea in Leipzig was 0.52 per hundred and in Vienna, 1.67 per hundred cases of cutaneous diseases. The frequency index (cases per month) was 0.54 for New York city and 9.7 for Berlin. Bolam [3] found that pityriasis rosea comprised 0.3 per cent of all dermatoses; Crocker,[6] 0.4 per cent; Kogoj and Farkas,[7]

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Read at the Sixty-Second Meeting of the American Dermatological Association, Inc., Monte-Bello, Quebec, Canada, June 1, 1939.

1. Cited by Little.[4]

2. Stelwagon, H. W., (*a*) cited by Little; [4] (*b*) Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1914, p. 203.

3. In discussion on Little.[4]

4. Little, E. G. G.: Discussion on Pityriasis Rosea, Proc. Roy. Soc. Med. **7**:121, 1914.

5. Benedek, T.: Statistiche Untersuchungen zur Kenntnis der Pityriasis rosea Gibert: I. Häufigkeit, Geschlecht, Lebensalter, Arch. f. Dermat. u. Syph. **170**: 581, 1934.

6. Crocker, H. R.: Diseases of the Skin, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1903, p. 408.

7. Kogoj, F., and Farkas, K.: Clinical Contribution on Pityriasis Rosea, Urol. & Cutan. Rev. **36**:451, 1932.

0.68 per cent; Glaubersohn,[8] 0.79 per cent; Pollitzer,[9] Gray[10] and Adamson,[11] each, 1 per cent; Lanz,[12] 2 per cent, and Pick,[13] 3 per cent. Ullmann,[14] in 1932, stated that the disease was becoming more frequent. The diagnosis of pityriasis rosea was made in 394 (1.29 per cent) of 30,604 new patients seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital in 1938.

II. AGE

Weiss, Lane and Showman[15] reported that 56.6 per cent of their 380 patients with pityriasis rosea were from 10 to 30 years of age. Most of Towle's[16] patients were from 20 to 30 years old, and Thibierge's,[1] from 15 to 35. Two thirds of Highman's and Rulison's[17] patients were from 20 to 40. Benedek[5] also found that pityriasis rosea was most common in persons between these ages but that the height of the frequency varied in different places. The majority of Chatschaturjan's[18] 146 patients were from 20 to 35 years old, while most of Kogoj's and Farkas'[7] patients were about 20. Eighty-seven of Szaboky's[19] 119 patients were from 15 to 40 years old, and 41 of Moingeard's[20] 56 patients were from 15 to 35. Glaubersohn[8] observed that the disease is more frequent in persons between 25 and 30 years of age. Ormsby[21] stated, "Most of the patients are young (fifteen to forty years of

8. Glaubersohn, S. A.: Pityriasis rosea, Dermat Wchnschr. **93**:1589, 1931.

9. Pollitzer, S.: Statistical Report of the American Dermatological Association for the Year 1916, J. Cutan. Dis. **36**:294, 1918.

10. Gray, (*a*) cited by Little;[4] (*b*) in discussion on Little.[4]

11. Adamson, H. W., in Allbutt, T. C., and Rolleston, H. D.: System of Medicine, New York, The Macmillan Company, 1911, vol. 9, p. 395.

12. Cited by Kogoj and Farkas.[7]

13. Pick, E.: Pityriasis Rosea, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 7, pt. 1, p. 401.

14. Ullmann, K.: Ueber die Natur der Pityriasis rosea: Ein kasuistisch-kritischer Beitrag, Dermat. Wchnschr. **95**:1153, 1932.

15. Weiss, R. S.; Lane, C. W., and Showman, W. A.: Pityriasis Rosea, Arch. Dermat. & Syph. **15**:304 (March) 1927.

16. Towle, H. P., (*a*) cited by Weiss, Lane and Showman;[15] (*b*) Recurrent Pityriasis Rosea, J. Cutan. Dis. **27**:364, 1909.

17. Highman, W. J., and Rulison, R. H.: Pityriasis Rosea: A Few Simple Facts, Arch. Dermat. & Syph. **7**:163 (Feb.) 1923.

18. Chatschaturjan, G.: Pityriasis rosea atypica, Dermat. Wchnschr. **93**:1772, 1931.

19. Szaboky, J.: Beiträge zur Aetiologie der Pityriasis rosea, Monatsh. f. prakt. Dermat. **43**:495, 1906.

20. Moingeard, A.: Etude sur le pityriasis rosé de Gibert, Thesis, Paris, no. 325, 1889.

21. Ormsby, O.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1934.

age)," and Bolam [3] considered pityriasis rosea a disease of youth; but Crocker [6] had a patient 70 years old, and Thomson and Cumings,[22] one 77 years old. Most of the patients of the latter authors were from 6 to 15 years of age. The ages of Savill's [3] patients ranged from 11 months to 50 years, and those of Adamson's,[11] from 2 to 60 years (the majority being from 15 to 30). The average age of 153 of our patients was 26.8 years. Thirty-eight per cent were from 20 to 35 years old. The youngest patient was 5 years old and the oldest 53.

III. SEX

The general opinion is that pityriasis rosea is twice as frequent in women as in men. Weiss, Lane and Showman [15] reported that 65 per cent of their patients were women and 35 per cent, men. This ratio of about 2 women to 1 man was the same for all ages and agrees with the reports of Towle,[16] Thibierge,[1] Moingeard [20] and Adamson [11] and almost agrees with that of Highman and Rulison.[17] However, 67 per cent of Szaboky's [19] 119 patients and 55 per cent of Chatschaturjan's [18] 146 patients were men and 71 per cent of Tandler's [23] 14 patients were men. Benedek,[5] Little,[4] Kogoj and Farkas,[24] Crocker [6] and Cunningham [25] found the incidence about equal in the two sexes. Fifty two and a half per cent of Thomson's and Cumings' [22] 156 patients and 80 per cent of Kirby-Smith's [26] were women. Pernet,[3] Glaubersohn,[8] Ormsby [21] and Simon [27] also found that pityriasis rosea was more frequent in women than in men. Of 199 of our patients 58.25 per cent were women and 41.75 per cent men.

IV. RACE

Pityriasis rosea is usually seen in white persons, but the occurrence of this eruption in Negroes has been reported by Weiss,[28] Gross,[29]

22. Thomson, M. S., and Cumings, J. N.: Investigations into the Causation of Pityriasis Rosea, Brit. J. Dermat. **43**:628, 1931.

23. Tandler, G.: Ueber Pityriasis rosea (Gibert), Arch. f. Dermat. u. Syph. **37**:127, 1896.

24. (*a*) Kogoj, F.: Pityriasis Rosea Haemorrhagica, Dermat. Wchnschr. **97**: 1261, 1933. (*b*) Kogoj and Farkas.[7]

25. Cited by Weiss, Lane and Showman.[15]

26. In discussion on Hazen, H. H.: Pityriasis Rosea: Late Observations on Etiology and Treatment, South. M. J. **24**:937, 1931.

27. Simon, C.: Quelques réflexions et souvenirs sur le pityriasis rosé de Gibert, Bull. méd., Paris **50**:702, 1936.

28. Weiss, L.: Pityriasis Rosea: An Erythematous Eruption of Internal Origin, J. A. M. A. **41**:20 (July 4) 1903.

29. Gross, E. R.: Pityriasis Rosea (Extensive Involvement), Arch. Dermat. & Syph. **37**:686 (April) 1938.

Stillians and Benedek [30] and Schiller.[31] Howard Fox [32] reported on 2,200 cases of cutaneous diseases in white persons and the same number in Negroes. He found pityriasis rosea in 7 (0.318 per cent) white patients and in 6 (0.272 per cent) Negroes. Schamberg [33] reported seeing pityriasis rosea in a mulatto. In discussion of this case, Davis [34] said that he and Knowles a few days previously had seen the disease in a mulatto woman. Corson,[35] Butterworth [36] and Klauder [37] observed that papular pityriasis rosea is more frequent in Negroes, and Guequierre [38] stated that the eruption is apt to be more severe and extensive in this race. Of the 380 patients seen by Weiss, Lane and Showman [15] in St. Louis, 24.2 per cent were Negroes. Of our 219 patients, only 2 were Negroes.

V. DURATION

In the first report on pityriasis rosea, Gibert [39] stated that the duration was from six weeks to two months, and Simon [27] observed that spontaneous healing occurred in six to twelve weeks. According to Ormsby,[21] "The affection runs its course ordinarily in from four to eight weeks, but may last for several months, if new lesions continue to appear." Adamson [11] found that the average duration was from five to eight weeks, and Pernet,[3] from three to four weeks. Duhring [40] and Jamieson [40] reported cases of "pityriasis perstans," and Weiss, 2 cases in which the lesions appeared and disappeared for over three

30. Stillians, A. W., and Benedek, T.: Leukoderma Following Pityriasis Rosea, Arch. Dermat. & Syph. **37**:103 (Jan.) 1938.

31. Schiller, A. E.: (*a*) Pityriasis Rosea in a Negro, Arch. Dermat. & Syph. **28**:127 (July) 1933; (*b*) Pityriasis Rosea, ibid. **31**:546 (April) 1935.

32. Fox, H.: (*a*) Observations on Skin Diseases in the Negro, J. Cutan. Dis. **26**:67, 1908; (*b*) cited by Weiss, Lane and Showman.[15]

33. Schamberg, J. F.: (*a*) A Case of Pityriasis Rosea in a Mulatto, J. Cutan. Dis. **27**:267, 1909; (*b*) in discussion on Friedman: Pityriasis Rosea Urticata, Arch. Dermat. & Syph. **26**:757 (Oct.) 1932.

34. In discussion on Schamberg.[33]

35. In discussion on Gross.[29]

36. Butterworth, T.: Pityriasis Rosea: Clinical Varieties and Etiology, Pennsylvania M. J. **38**:402, 1935.

37. Klauder, J. V.: Pityriasis Rosea, with Particular Reference to Its Unusual Manifestations, J. A. M. A. **82**:178 (Jan. 19) 1924.

38. Guequierre, J. P., (*a*) in discussion on Gross;[29] (*b*) Pityriasis Rosea, Associated with Oral Lesions, Arch. Dermat. & Syph. **38**:262 (Aug.) 1938; (*c*) 159 (July) 1938.

39. Gibert, C. M.: Traité pratique des maladies spéciales de la peau, ed. 3, Paris, G. Bailliére, 1860, p. 402.

40. Cited by Butterworth.[36]

years. Vidal [41] reported a case in which the condition lasted six months, while in Bailey's [42] case the skin was entirely clear in twelve days. Bronson,[1] Montgomery,[25] Crocker,[6] Phillips,[25] Franck,[43] Tenneson [1] and Savill [3] have reported cases in which the condition persisted for several months. In Hallopeau's [44] case and in Fournier's [45] the eruption lasted four years. Little had 3 cases in which the condition lasted for only two weeks and several in which it lasted for three weeks, but in 1 it persisted for five to six months. He found that the usual duration was from five to six weeks. The average duration in our 26 control cases was four and seven-tenths weeks.

VI. SEASONAL INCIDENCE

There is great variation in the reports in the literature as to the season when pityriasis rosea is most prevalent. Adamson [11] found that the seasonal incidence varied from year to year. Weiss, Lane and Showman [15] found pityriasis rosea most frequent in the spring and fall. In the series which they compiled from the literature and in their own cases, the incidence was greatest in January, high from September to May and lowest in July. Ormsby [21] stated that "without question pityriasis rosea is more common in the spring and in the autumn than in other seasons." Most of Towle's [16] cases occurred in the autumn; and Thomson and Cumings [22] and Little [4] encountered most of their cases in October, but 63 per cent of Moingeard's [20] 56 cases and the majority of Bazin's [25] were observed in the spring. Kogoj and Farkas [24] encountered the fewest cases in summer and early winter, while Simon's [27] cases were more frequent in warm weather. Gibert [39] also observed that pityriasis rosea is most frequent in the hot months, but Little,[4] Whitfield,[8] Pernet [3] and Savill [3] noted more cases in the winter. Gray [10] and Whitfield [8] both noticed that there were more cases than usual in the cold damp summer of 1912. Most of the cases reported by Highman, Rulison and Fox [32b] occurred from December to March. Glaubersohn [8]

41. Vidal, E., (*a*) cited by Weiss, Lane and Showman; [15] (*b*) Du pityriasis circinéet et marginé: Description de son mycoderme, le microsporon anomœon (microsporon dispar), Ann. de dermat. et syph. **3**:22, 1882.

42. Bailey, H.: Pityriasis Rosea: Report of a Case with Lesions of the Palms and Soles, Arch. Dermat. & Syph. **32**:104 (July) 1935.

43. Franck, G.: Pityriasis rosé de Gibert atypique, Schweiz. med. Wchnschr. **12**:709, 1931.

44. Hallopeau, (*a*) cited by Little; [4] (*b*) cited by Friedman: Pityriasis Rosea Urticata, Arch. Dermat. & Syph. **26**:757 (Oct.) 1932; (*c*) cited by Greenhouse, C., and Cornell, V. H.: Pityriasis Rosea: Report of a Case Showing a Gigantic Herald Placque with Unusual Manifestations, ibid. **28**:823 (Dec.) 1933.

45. Cited by Friedman: Pityriasis Rosea Urticata, Arch. Dermat. & Syph. **26**: 757 (Oct.) 1932.

found pityriasis rosea least frequent in the fall. Little [4] noticed a rise in the frequency of pityriasis rosea in July, October and December. Szaboky,[19] Fiocco [25] and Crocker [6] noted no seasonal variation. In 78 (38 per cent) of 203 of our cases the condition started in the fall, in 59 in the winter, in 38 in the spring and in 28 in the summer.

VII. SYSTEMIC SYMPTOMS AND ETIOLOGIC BACKGROUND

Ormsby [21] stated, "Mild constitutional disturbance exhibited as headache, moderate elevation of temperature, congestion of the fauces and slight enlargement of submaxillary and cervical glands may accompany an acute widespread eruption." He has found that many patients with pityriasis rosea have light hair and delicate skins and have been enfeebled by physical fatigue and overwork in school. Simon [27] also found pityriasis rosea more frequent in patients with fine skin and blond hair. In 42.3 per cent of Gourvitch's [46] 85 cases and in 50 per cent of Szaboky's [19] cases there were prodromal symptoms of malaise, headache, chills and fever. Thomson and Cumings [22] observed slight fever (maximum 100 F.) in 6 of 18 cases; in 2 of them there was arthralgia and in 2 dyspepsia. Little [4] stated the belief that general glandular enlargement occurs in the majority of cases. MacLeod [3] said that general symptoms are not infrequent, but the general health of Adamson's [11] patients was good. Alderson [47] noted definite, severe nervous stress from prolonged, excessive mental work, worry or actual shock in 10 of 11 cases studied. Only 2 of our 219 patients complained of any prodromal symptoms. One had malaise and sore throat, and 1 had vomiting and diarrhea.

VIII. RELATION OF INFECTION OF THE TONSILS TO PITYRIASIS ROSEA

Pernet,[3] Dore [3] and MacLeod [3] frequently found involvement of the tonsils and general glandular enlargement in patients with pityriasis rosea. Twelve of Owen's [48] 30 patients had infection in the upper part of the respiratory tract or in the tonsils. About 50 per cent of Mestchersky's [49] patients complained of sore throat. Wile [48] declared that

46. Gourvitch, E. I.: Sur la clinique, la pathogénie et le traitement du pityriasis rosé de Gibert: Pityriasis rosea Gibert, Ann. de dermat. et syph. **7**:488, 1936.

47. Alderson, H.: Pityriasis Rosea: Clinical Observations, J. Cutan. Dis. **32**: 353, 1914.

48. Cited by Hazen, H. H.: Pityriasis Rosea: Late Observations on Etiology and Treatment, South. M. J. **24**:937, 1931.

49. Mestchersky, G.: Contribution à l'étiologie du pityriasis rosé de Gibert, Bull. Soc. franç. de dermat. et syph. **33**:148, 1926.

pityriasis rosea apparently occurs only in persons who still have their tonsils, and he often found enlarged lymph glands in patients with this disease. Haspel [50] had 6 patients with pityriasis rosea and infected tonsils. In each case the eruption disappeared in one to four days after tonsillectomy. Hazen [51] found the tonsils or lymphoid structures of the throat diseased in 94 per cent of 70 patients with pityriasis rosea. Four patients had recurrent attacks of the eruption, each of which was associated with a definite follicular tonsillitis. The diseased tonsils or lymphoid tissue in the throat was present in only 20 per cent of 300 control patients with other cutaneous diseases. From these observations Hazen assumed that the portal of entry in pityriasis rosea probably is the tonsils. An exactly opposite opinion was expressed by Weiss,[52] who said that there is no direct association between pityriasis rosea and diseased tonsils, and by Kirby-Smith [31a] and Highman,[26] who both stated that they had never found infections of the throat associated with pityriasis rosea. Only 5 of Thomson's and Cuming's [22] 18 patients showed any faucial congestion; only 1 had symptoms referable to the throat, and only 3 had any adenopathy. In only 2 of these 3 were the cervical glands enlarged. None of our patients complained of sore throat, but the throat was examined in only a few.

IX. CONTAGION AND OCCURRENCE OF MORE THAN ONE CASE IN THE SAME HOUSEHOLD

Lord [53] reported the simultaneous appearance of pityriasis rosea in 2 members of his own family. His son had a typical generalized pityriasis rosea, and his wife, a characteristic herald plaque. In a review of the literature he cited 18 other instances of pityriasis rosea apparently occurring as a result of close association. Haas [54] had pityriasis rosea himself, and a few days later the same disease developed in his wife, his mother, his baby and the baby's nurse. Fourteen days after he took care of a patient with pityriasis rosea, a herald patch developed at the site of a trauma on Edelston's [55] own skin. Zeisler [1] had pityriasis rosea himself, and two weeks later his wife had the same eruption. Kurtz

50. Haspel, K. L.: Angaben zur Aetiologie der Pityriasis rosea, Dermat. Wchnschr. **102**:357, 1936.

51. Hazen, H. H.: Pityriasis Rosea: Late Observations on Etiology and Treatment, South. M. J. **24**:937, 1931.

52. Weiss, R. S., (*a*) in discussion on Hazen; [51] (*b*) in discussion on Weiss, Lane and Showman.[15]

53. Lord, L. W.: Etiology of Pityriasis Rosea, Arch. Dermat. & Syph. **26**:981 (Dec.) 1932.

54. Haas, A.: Identität von Herpes tonsurans und Pityriasis circinata (?), Berl. klin. Wchnschr. **17**:259, 1882.

55. Cited by Thomson and Cumings.[22]

and Davis,[56] medical students who worked but did not room together, contracted pityriasis rosea within one week of one another. Weiss, Lane and Showman [15] reported 2 instances of pityriasis rosea in the same family; in one family a girl and her brother had the disease, and in the other, a woman and her son. Two cases in the same household have been reported also by Photinos,[57] Fordyce,[58] Peroni,[48] Horand,[1] Crocker,[6] Fox [59] and Wile.[25] Butterworth [36] stated that he had seen 2 or more cases in the same household on more than twenty occasions, but none of Hazen's [40] 150 cases were in the same home. Little [4] found only 1 instance of infectivity in 174 cases. Pernet [3] found no instances of contagion in his series of cases, and this was also our experience.

X. ETIOLOGIC AGENTS: BACTERIA, FUNGI AND THE WEARING OF NEW, UNWASHED OR DAMP CLOTHING

In 1882 Vidal [41b] discovered a microsporon in lesions of pityriasis rosea. This finding was confirmed by Ferrari [48] and Du Bois; [60] and Gougerot [61] stated that these spores are the cause of the disease and that they are similar to blastomycetes. In 1889 Kaposi [48] and Newman [48] discovered mycelia. Photinos [57] found spores in each of 4 cases studied. They were also found by Covisa [62] and Nékám.[1] Joyeux and Burnier [63] demonstrated spores in scales from a patient with typical pityriasis rosea after injections of tréparsol (the sodium salt of 4-formylamino-4-hydroxyphenylarsenic acid). Joyeux, Burnier and Duché [64] observed spores in 28 of 30 cases but were unable to cultivate them or to produce the disease by injecting solution made with the scales into other patients. Thomson and Cumings [22] and Whitfield [3] stated the belief that these so-called spores are merely fluid artefacts. Brocq [65]

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56. Kurtz, F. H., and Davis, J. B.: Pityriasis Rosea: An Account of Suggested Contagiousness and of Attempted Experimental Transmission, Arch. Dermat. & Syph. **28**:13 (July) 1933.

57. Photinos, P.: Beitrag zur Natur der Pityriasis rosea, Dermat. Ztschr. **68**: 187, 1934.

58. Fordyce, J. A.: A Case of Pityriasis Rosea, J. Cutan. Dis. **14**:356, 1896.

59. Fox, G. H.: Pityriasis Rosea, J. Cutan. Dis. **16**:340, 1898.

60. Du Bois: Parasite cryptogamique des dermatoses erythemato-squameuses du type pityriasis rosé de Gibert, Ann. de dermat. et syph. **3**:32, 1912.

61. Gougerot, H.: Traitement du pityriasis rosé de Gibert par l'éosine, Bull. Soc. franç. de dermat. et syph. **44**:1708, 1937.

62. Covisa, J. S.: Pityriasis rosea Gibert, Dermat. Wchnschr. **56**:115, 1913.

63. Joyeux and Burnier: A propos d'un cas de pityriasis rosé, Bull. Soc. franç. de dermat. et syph. **36**:1054, 1929.

64. Joyeux, Burnier and Duché: Recherches sur la nature mycosique du pityriasis rosé, Bull. Soc. franç. de dermat et syph. **37**:1128, 1930.

65. Brocq, B., (*a*) cited by Simon; [27] (*b*) Note sur la plaque primitive du pityriasis rosé de Gibert, Ann. de dermat. et syph. **8**:615, 1887.

was of the opinion that the disease is passed along by an insect bite, probably that of a flea, but Simon [27] rarely obtained a history of flea bites from his patients and stated the belief that pityriasis rosea is due to a filtrable virus. Thomson and Cumings [22] agreed with this opinion. Benedek [66] considered pityriasis rosea due to a constant endoparasitism of Schizosaccharomyces hominis and produced by a hematogenous infectious route. He stated the belief that the parasite is carried by the blood into skin which is already allergized and that it then decomposes in the lesion itself through the immune powers of the macrophage. He considered this theory proved by the presence of the primary mycotic focus, the specific allergy and the parasite in the blood and cutaneous lesions during the exanthem. He attributed the inability to transmit or produce the disease to the fact that every person, because of the constant endoparasitism, has an immunity against a superimposed infection due to Schizosaccharomyces. Thomson and Cumings [22] were unable to find Benedek's organisms in cultures of blood or blister fluid from the herald patch, and Pernet [3] could find no fungi of any type in the scales. Oppenheim [67] reported that pityriasis rosea is due to a ringworm organism which enters through the herald patch, from which spores appear in the blood, and that the secondary lesions are due to embolic thrombi in the fine capillaries of the skin. Hebra [67] and Kaposi [48] have also stated the belief that the disease is due to a ringworm-like parasite.

Many German authors, especially Lassar,[68] have declared that pityriasis rosea is due to the wearing of new, unwashed or damp garments. Veiel [69] reported several cases in which the disease apparently occurred after the wearing of new or damp linen, and Wise and Sulzberger [70] have commented on the frequency of this association. Parkhurst [25] often observed in the history of a patient that the disease occurred after wearing clothing which had been stored in a damp, dark place, and he expressed the opinion that it is due to contact with some organism which grows in such places. Kogoj and Farkas [7] reported a case in which the herald patch on the left knee appeared shortly after the patient had worn new trousers over short underwear and another case in which the eruption appeared two weeks after the wearing of a sweater which had lain in a wardrobe during the summer. Heath [3]

66. Benedek, T.: Schizosaccharomycosis: II. Clinical (Mycide) Forms; Pityriasis Rosea of Gibert; Its Etiology and Pathogenesis, Arch. Dermat. & Syph. **26**:397 (Sept.) 1932.

67. Cited by Lord.[58]

68. Lassar, O.: Ueber die Natur der Pityriasis rosea, Deutsche med. Wchnschr. **18**:469, 1892.

69. Veiel, F.: Zur Kenntnis der Pityriasis rosea, Dermat. Ztschr. **62**:91, 1931.

70. Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1931, p. 154; 1934, p. 565.

reported a case in which pityriasis rosea occurred in a boy two days after he had worn a fresh flannel vest while running a race. Thomson and Cumings [22] stated the belief that the herald patch is almost always on the trunk because there the clothes most closely touch the body. Le Damany [55] expressed the unique opinion that pityriasis rosea is a tuberculid. Only 32 (19.05 per cent) of the 168 of our patients gave a history of wearing new or damp clothing shortly before the appearance of the eruption. In obtaining this history, however, we questioned the patient only about clothing worn over the site of the herald patch, and this may account for the relatively low percentage.

XI. LABORATORY INVESTIGATIONS

Milian and Périn [71] cultured streptococci from dyshidrotic vesicles on the hands of a boy who had bullous impetigo and pityriasis rosea and questioned whether the latter disease was not also due to a streptococcus. In all of 20 patients with pityriasis rosea Périn [72] obtained a positive reaction with a streptococcus vaccine. Three normal persons and 8 patients with other dermatoses gave a negative reaction. A year later, with the assistance of Michaux and Cottet, Périn [73] confirmed this work. Gourvitch [46] also stated the belief that pityriasis rosea is of streptococcic origin. Of his 55 patients only 4 failed to react to intradermal injections of streptococcus vaccine, while 50 gave no reaction to staphylococcus vaccine. A series of control patients all gave negative reactions to streptococcus vaccine. Examination of the blood of 28 of his patients showed lymphocytosis in 8 and eosinophilia in 9. Examinations for tinea, trichophytin tests and injections of a solution made from the scales into normal men and animals all gave negative results. Examination of the blood of Milian's [74] patient revealed 7 per cent eosinophils. Thomson and Cumings [22] found no consistent organisms in cultures of smears from the throat or feces, and all examinations of the urine gave negative results. They discovered a "definite tendency towards leucopenia with relative lymphocytosis." With intradermal injections of an extract of scales from a herald patch in saline solution, they obtained only two negative reactions in 13 healthy persons, one negative in 5 patients with other dermatoses and only one positive and two very weakly positive reactions in 10 patients with pityriasis rosea.

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71. Milian, G., and Périn, L.: Trisyndrome, Bull. Soc. franç. de dermat. et syph. **38**:852, 1931.

72. Périn, L.: Pityriasis rosé de Gibert et intradermo-reactions au vaccin streptococcique, Bull. Soc. franç. de dermat. et syph. **35**:795, 1928.

73. Périn, L.; Michaux, L., and Cottet, J.: Intradermo-reactions streptococciques dans le pityriasis rosé de Gibert, Rev. franç. de dermat. et de vénéréol. **5**:3, 1929.

74. Milian, G.: Pityriasis rosé de Gibert à croutes impetiginiformes, Rev. franç. de dermat. et de vénéréol. **5**:15, 1929.

XII. ATTEMPTS TO PRODUCE PITYRIASIS ROSEA EXPERIMENTALLY

Wile [75] produced a blister on a herald plaque by the application of a cantharides plaster and injected fluid from the blister percutaneously and by scarification. After several failures, he was finally able to produce an explosive form of pityriasis rosea in 3 patients who were inoculated and in 1 who was scarified. Owens [25] and Thomson and Cumings [22] were unable to produce pityriasis rosea by inoculation of scales from the lesions. Many other attempts also have been unsuccessful. Kurtz and Davis [56] injected intradermally filtrates of a saline solution suspension of scrapings from a herald spot into patients with acute pityriasis rosea and into others convalescing from the disease. In 15 of 18 patients in four hours there was a local, circumscribed hyperemia, which disappeared in twenty-four hours. There were no positive reactions in definitely convalescent patients or in healthy persons, and no lesions resembling pityriasis rosea developed. These authors also removed typical secondary lesions of pityriasis rosea with a curet and made a suspension of them in Ringer's solution, which they injected intradermally into clear areas of their own skin while they had the eruption and into the skin of 2 healthy persons and of 2 rabbits. No local reaction occurred in themselves, in the healthy persons or in the rabbits.

XIII. LOCATION OF ERUPTION

Lesions of pityriasis rosea may occur on any part of the body, but they are most frequent and numerous on the trunk. In Weiss's, Lane's and Showman's [15] cases, the trunk was involved in 72.2 per cent, the arms in 39.3 per cent, the thighs in 33.4 per cent, the neck in 17.3 per cent, the face in 7.9 per cent, the shoulders in 7.3 per cent, the legs in 4.4 per cent, the feet in 3 per cent, the buttocks in 2.3 per cent, the forearms in 2.3 per cent, the axillas in 2.1 per cent, the hands in 1.8 per cent and the genitocrural region in 1.2 per cent. In almost 10 per cent the eruption was generalized. Little [4] had a patient with lesions on the whole surface of the skin except the hands and feet. Duhring,[1] Little,[4] Howard Fox [32b] and Chatschaturjan [18] have reported cases in which there were lesions on the penis. In 179 of our patients the eruption was on the trunk in 91 per cent, the extremities in 86.6 per cent, the neck in 59.8 per cent, the face in 19.6 per cent and the scalp in 3.9 per cent.

XIV. LOCALIZED FORMS

Dore [8] and Klauder [76] expressed the opinion that localized forms of pityriasis rosea are not uncommon and tend to last longer than a gen-

75. Wile, U. J.: Experimental Transmission of Pityriasis Rosea, Arch. Dermat. & Syph. **16**:185 (Aug.) 1927.

76. In discussion on Weiss, Lane and Showman.[15]

eralized eruption. Butterworth [36] observed that localized pityriasis rosea usually is seen in the groins and in the axillas. He mentioned the so-called "inverted pityriasis rosea" in which the lesions are limited to the extremities. Pityriasis rosea limited to the face and neck has been reported by Little,[4] Moingeard,[20] Photinos [57] and Towle.[16a] Szaboky,[19] Moingeard [20] and Klauder [37] have described unilateral distribution of pityriasis rosea. Little [4] reported a case with lesions only on the thighs and another with the eruption limited to the right hip, buttock and thigh. Costello [77] reported an eruption of pityriasis rosea exactly limited to an area covered by bathing trunks and to the axillas and the upper inner aspect of the arms, which appeared about six months after acquiring a deep tan on the rest of the body. He also mentioned a woman who had been treated with roentgen rays for a dermatosis involving the left side of the chest. Later profuse pityriasis rosea developed, but the previously irradiated areas were completely spared. In 179 of our patients the eruption was limited to the neck in 2 and to the abdomen in 1.

XV. TYPES OF LESIONS

In the majority of cases of pityriasis rosea the eruption consists of macules, but often papules and occasionally other lesions are present. Benedek [78] described ten types of lesions seen in pityriasis rosea: macules, papules, maculopapules, urticarial papules, vesicles, lichenoid lesions, small red hemorrhagic spots, lesions resembling lichen planus, lesions like erythema multiforme and lesions resembling chronic lichenoid pityriasis. On examination of 1,556 cases in the literature, he concluded that there is only one typical lesion, the macule. In the cases reported by Weiss, Lane and Showman [15] macules were present in 76.1 per cent, papules in 7.9 per cent, mixed papules and plaques in 13.1 per cent and circinate lesions in 2.7 per cent. Vesicles were seen in 2 cases.

XVI. ATYPICAL FORMS

Fourteen (9.5 per cent) of Chatschaturjan's [18] 146 cases of pityriasis rosea were atypical. In one group the eruption started with maculopapular lesions, the size of a pinhead, which were more numerous on the neck and chest than on the trunk. In the second group first there was severe itching, which was followed by an urticarial and papulovesicular eruption with infiltrated lesions, some of which resembled scabies and some, erythema multiforme. In both groups typical lesions appeared after a few days. Weiss, Lane and Showman [15] commented on the fact

77. Costello, M. J.: Pityriasis Rosea Sparing Tanned Areas of the Skin (Bathing Trunk Distribution), Arch. Dermat. & Syph. **38**:75 (July) 1938.

78. Benedek, T.: Statistische Untersuchungen zur Kenntnis der Pityriasis rosea Gibert, Acta dermat.-venereol. **17**:151, 1936.

that pityriasis rosea has multiform lesions, and Klauder [79] described nine distinct varieties. Wirz,[12] Schweitzer [40] and Kogoj [24a] have reported cases of pityriasis rosea with small red hemorrhagic points, and Klauder [76] has noticed a recent increase in "pityriasis rosea hemorrhagica." Vesicular pityriasis rosea has been described by Little,[4] Fox [25] and Wile.[25] Weiss [52b] and Butterworth [36] expressed the opinion that this type lasts longer than the common type. Ullmann [14] had 1 patient with vesicles on the soles, 1 with hyperkeratotic eczematoid changes on the soles, toes and finger tips and deep, scaly infiltrations on the palms, and another with vesicles which later became pustules. He said that he had seen more atypical and severe forms lately. Sobel [80] presented a patient with a generalized eruption of pink macules, some of which were topped with vesicles; and Weiss [28] reported on a patient who had small plaques capped with a clear vesicle. Becker and Ritchie [81] had a patient with pityriasis rosea, with papules and superficial vesicles on the trunk, arms and thighs. They commented that there are microscopic vesicles in many cases and that probably macroscopic vesicles are merely an exaggeration of this process. Klauder [76] said that vesicular pityriasis rosea is unusual. Adamson [11] stated that the vesicular type is especially frequent in infants and children, but this is not the general opinion, although Weiss [52b] has found that pityriasis rosea in children is chiefly papular and vesicular. Blaschko's [40] patient had bullae on the mucous membranes. Kiess [82a] described 2 cases of pityriasis rosea with many pustular lesions; in the first the pustules followed bullae, and in the second the lesions were pustular from the onset. In 2 cases reported by Weiss, Lane and Showman [15] and in Becker's and Ritchie's [81] case, the eruption at first resembled varicella and later became typical of pityriasis rosea. Kiess [82b] reported 2 cases of "pityriasis rosea pustulocrustosa." Milian [74] described a case of pityriasis rosea with medallions and papules, many of which were covered with yellow dry, adherent crusts. Little [4] had a patient with an itchy, almost universal eruption which was followed by marked scaling and another patient with an extensive eruption consisting of many extremely itchy follicular maculopapules. Howard Fox's [32b] patient also had follicular papules. Vidal [41b] first described "pityriasis circiné et marginé," which is now generally accepted as a type of pityriasis rosea characterized by its long duration.

79. In discussion on Friedman.[85]

80. Sobel, N.: Pityriasis Rosea with Vesicles, Including the Face, Arch. Dermat. & Syph. **38**:466 (Sept.) 1938.

81. Becker, S. W., and Ritchie, E. B.: Pityriasis Rosea (Vesicular), Arch. Dermat. & Syph. **23**:779 (April) 1931.

82. Kiess, O.: (*a*) Weiterer Beitrag zur Kenntnis der Pityriasis rosea palmaris et plantaris, Dermat. Wchnschr. **96**:368 1933; (*b*) Pityriasis rosea, Pityriasis rosea et pustulo-crustosa, ibid. **92**:945, 1931.

Duhring [83] and Colcott Fox [84] reported cases of "pityriasis rosea maculata et circinata;" and Darier,[25] Pringle,[25] Nékám [1] and Klauder [87] reported cases of "pityriasis rosea gigantea," with palm-sized symmetric plaques and circles on the body. Friedman [85] presented a case with extremely itchy, red, raised urticarial lesions. Both Savill [3] and Little [4] had cases of this type which was first described by Hallopeau [44b] in 1906, as the "forme ortiée," and later by Vorner.[45] Dore [3] has found that in many patients the eruption is urticarial. According to Butterworth,[36] the urticarial factor is most marked at the onset of the eruption. Stokes [79] and Gourvitch [46] agreed that a highly nervous patient has a much more florid urticarial type of pityriasis rosea. None of our patients had atypical lesions except 2 who had several urticarial wheals.

XVII. LESIONS ON THE SCALP AND FACE

Butterworth [36] stated that "The only recorded instance in which pityriasis rosea involved the scalp in an adult was Gager's case in a female, age 35," [40] but Kumer,[12] Weiss,[28] Horand,[1] Adamson,[11] Haxthausen,[86] Fuhs,[12] Kerl,[12] Oppenheim,[12] Pick,[13] Dufke [12] and Balina [87] have described lesions on the scalp. Cole [88] stated that there is greater tendency for pityriasis rosea to involve the scalp in children than in adults, and Haxthausen asserted that the scalp is almost always involved in pityriasis rosea in children. In the first case reported by Weiss, Lane and Showman [15] the lesions first appeared on the face and later on the scalp, and both these areas were involved in their fourth case. Guequierre [38a] commented that in the last few years he had observed several patients with lesions on the neck and scalp, and Knowles [35] agreed that recently he has noticed lesions extending to the neck and the lower part of the face. Barney's [89] patient had many lesions on the face and scalp; and Montgomery and Culver,[90] Stowers,[25] Stillians and Benedek,[30]

83. Duhring, L. A.: Pityriasis Maculata et Circinata, Am. J. M. Sc. **80**:359, 1880.

84. Fox, C.: On the Disease of the Skin Named Pityriasis Maculata et Circinata, Lancet **2**:485, 1884.

85. Friedman: Pityriasis Rosea Urticata, Arch. Dermat. & Syph. **26**:757 (Oct.) 1932.

86. Haxthausen, H.: Pityriasis Rosea of the Scalp, an Almost Invariable Location of the Disease in Children, Brit. J. Dermat. **39**:141, 1927.

87. Balina, P. L.: Pitiriasis rosada de Gibert familiar: Tres casos simultáneos; consideraciones, Semana méd. **2**:1169, 1927.

88. In discussion on Barney, R. E.: Pityriasis Rosea Involving the Scalp, Arch. Dermat. & Syph. **25**:190 (Jan.) 1932.

89. Barney, R. E.: Pityriasis Rosea Involving the Scalp, Arch. Dermat. & Syph. **25**:190 (Jan.) 1932.

90. Montgomery, D. W., and Culver, G. D.: Pityriasis Rosea: Two Unusual Cases, Arch. Dermat. & Syph. **12**:257 (Aug.) 1925.

Sobel [80] and Gross [29] have presented patients with lesions on the face. In Friedman's [85] patient the herald plaque was on the chin, and the generalized eruption started on the face and spread downward. Szaboky [19] had a patient with lesions on the eyelids. Klauder [79] stated the belief that lesions are rare on the face but not on the neck. We were surprised at the large number of our patients who had lesions on the face (19.55 per cent) and on the scalp (3.91 per cent) and agree with the comments of several authors that lesions on these areas have become more frequent recently.

XVIII. LESIONS ON THE HANDS AND FEET

Szaboky [19] stated that pityriasis rosea never occurs on the hands and feet, but cases in which there were lesions on the palms and soles have been reported by Rille,[12] Ullmann,[14] Schamberg,[12] Conrad,[12] Balban,[12] Little,[4] Benedek,[91] Fessler,[12] Kerl,[12] Kren,[12] Oppenheim,[12] Kiess,[82] Volk,[12] Moingeard,[20] Parkhurst,[92] Klauder,[93] Stowers [25] and Rosen.[94] Weiss, Lane and Showman [15] reported that in 1.8 per cent of their cases the lesions were on the hands and in 3 per cent on the feet. In 1 of their cases the lesions were on the palms and soles, resembling those of pompholyx. Duhring [40] and Fox [25] reported on patients with lesions on the dorsa of the hands, and Wright's [95] and Moingeard's [20] had lesions on the dorsa of the feet and in the webs of the fingers. Kogoj and Farkas [7] observed that the soles are less often affected than the palms. Combes described five forms in which pityriasis rosea appears on the hands and feet: (1) discrete, scaly red plaques; (2) livid red, slightly elevated and infiltrated maculopapules, with tiny vesicles on the thin-skinned portions of the fingers and toes; (3) scaly red patches on the inner surfaces of the palms and soles intermingled with vesicles; (4) closely arranged dyshidrotic vesicles resembling sago grains, and (5) universal redness and scaling of the palms and soles. He reported a case [96] in which deep, dusky red lesions with a collarette of scales, which resembled syphilids, were on the palms and soles and papules were on the forearms, wrists and dorsa of the hands. Bailey [42] reported a typical case of pityriasis rosea in which there were similar

91. Benedek, T.: Bezuglich Pityriasis Rosea Gibert, Dermat. Wchnschr. **86**:90, 1928.

92. In discussion on Schiller.[31a]

93. Klauder, J. V.: Pityriasis Rosea, Arch. Dermat. & Syph. **19**:523 (March) 1929.

94. In discussion on Sobel.[80]

95. Wright, C. S.: Pityriasis Rosea of Unusual Distribution, Arch. Dermat. & Syph. **26**:757 (Oct.) 1932.

96. Combes, F. C.: Pityriasis Rosea: Report of a Case with Lesions of the Palms and Soles, Brit. J. Dermat. **44**:586, 1932.

itchy lesions, resembling syphilids, on the palms and soles. Haldin-Davis'[97] patient also had lesions on the palms similar to syphilids, but the soles were clear and the Wassermann reaction of the blood was negative. Weber's and Rattner's[98] patient had typical pityriasis rosea on the trunk and lesions on the palms and soles which resembled those of vesicular ringworm but in which no fungi were found. Milian's and Périn's[71] patient had dyshidrotic vesicles on the hands and the sides of the fingers, and Milian's[99] patient had dyshidrotic bullae on the same areas. Keim[92] stated that he had "often seen typical pityriasis rosea on the trunk associated with a dyshidrotic type of eruption on the hands and feet." Three of our patients had lesions on the feet and 1, on the hands, but none of them had lesions on both the hands and the feet.

XIX. LESIONS ON THE MUCOUS MEMBRANES

Guequierre[38b] presented a boy with typical pityriasis rosea on the trunk and a superficial eroded lesion on the right buccal mucosa. In the discussion of this case he stated that he had found oral lesions in 3 of 8 patients with pityriasis rosea seen in the previous week and a half. He also presented a girl[38c] with a painless annular lesion which had a red border and a slightly depressed, somewhat scaly center on the right buccal mucosa and which resembled the typical lesions of pityriasis rosea on her skin. In the discussion of this case the diagnosis of the spot in the mouth was disputed. Wile[100] described a case in which first bullae appeared on the oral, nasal and vaginal mucosa and later typical lesions developed. Hazen[40] reported a case in which there were lesions on the mucous membranes, and Rosen[94] saw a patient with lesions on the tongue. Thomson and Cumings[22] found no lesions on the mucous membranes of 18 patients. We saw no patients with lesions on the mucous membranes.

XX. INCIDENÇE OF HERALD PLAQUE

The reports of various authors vary greatly regarding the incidence of the herald plaque. MacLeod[3] and Heath[2] stated that it is usually present, while Ullmann[14] considered it rare. Whitfield[3] stated the

97. Haldin-Davis, H.: Pityriasis Rosea with Lesions on Palms, Brit. J. Dermat. **45**:71, 1933.

98. Weber, L. F., and Rattner, H.: Clinical Variants of Familiar Diseases of the Skin: Phenolphthalein Eruption; Pityriasis Rosea; Lichen Planus; Parapsoriasis, Arch. Dermat. & Syph. **28**:190 (Aug.) 1933.

99. Milian, G.: Pityriasis rosé à plaque initiale anormale et géante et accompagné de dysidrose, Rev. franç. de dermat. et de vénéréol. **12**:81, 1936.

100. In discussion on Shaffer, L. W.: A Case for Diagnosis (Pityriasis Rosea?), Arch. Dermat. & Syph. **25**:766 (April) 1932.

belief that the history of a herald patch is suggested to the patient and that it is really not as frequent as is usually thought. Pernet [3] considered the herald patch an important diagnostic feature of the disease. It appeared in 12 per cent of Towle's [16a] cases, 27 per cent of Owen's,[25] 27 per cent of Weiss, Lane and Showman's,[15] 50 per cent of Szaboky's,[19] 54 per cent of Montgomery's [25] and 94 per cent of Highman and Rulison's.[17] Thomson and Cumings [22] observed the herald patch in 15 (83 per cent) of 18 cases, but Weiss,[52b] in only 2 (14 per cent) of 14, and Little,[4] in only 19 (11 per cent) of 174. A herald patch was noted in 90 (51.72 per cent) of 174 of our cases.

XXI. THE INTERVAL BETWEEN THE APPEARANCE OF THE HERALD SPOT AND THAT OF THE GENERALIZED ERUPTION

The interval between the appearance of the herald spot and that of the generalized eruption, which Weiss, Lane and Showman [15] termed "the secondary incubation period," was four days or less in 18 (40 per cent) of their 45 cases. The longest period was forty-seven days. Finnerud [101] stated that in about 75 per cent of patients the herald spot appears four to ten days before the generalized eruption. Brocq [65b] found this interval to be four to fifteen days; Adamson,[11] ten days; and Pernet,[3] about one week. Little [4] discovered no apparent incubation period in more than half his cases. The incubation period was from two to fourteen days in his other cases, one week in Finnerud's [101] and in Reuter's [102] case, two weeks and nine days respectively in Shellow's [103] 2 cases, three weeks in Gross's [29] case and one month in Kogoj and Farkas',[7] five weeks in 1 of Thomson and Cumings' [22] cases, six weeks in Moingeard's [20] case and two months in Hallopeau's,[44c] four to five months in Greenhouse and Cornell's [104] and six months in Schiller's.[31b] The shortest interval reported in the literature was in Friedman's [85] case, in which the herald spot on the chin was followed in three hours by lesions on the face and four hours after this by an eruption on the neck, chest and abdomen. In 77 of our cases the generalized eruption appeared on an average of one and a half weeks after the herald patch was first seen. The shortest interval was one day, and the longest, eight weeks.

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101. Finnerud, C. W.: Pityriasis Rosea, M. Clin. North America **13**:457, 1929.

102. Reuter, M. J.: Thrombophlebitis and Pityriasis Rosea, Arch. Dermat. & Syph. **35**:1137 (June) 1937.

103. Shellow, H.: Unusual Location of Herald Plaque of Pityriasis Rosea, Arch. Dermat. & Syph. **32**:106 (July) 1935.

104. Greenhouse, C., and Cornell, V. H.: Pityriasis Rosea: Report of Case Showing a Gigantic Herald Plaque with Unusual Manifestations, Arch. Dermat. & Syph. **28**:823 (Dec.) 1933.

XXII. LOCATION OF THE HERALD PLAQUE

The herald plaque is usually located on the trunk, but several reports of unusual sites are recorded in the literature. Both Guequierre [38a] and Knowles [35] have stated that in the last few years they have observed several cases in which the herald plaque was in an unusual site; and Guequierre saw 1 patient with the herald plaque on the dorsum of the foot. The site of the herald plaque in eighty-six of Weiss', Lane's and Showman's [15] cases was the anterior wall of the chest in 31, the arms in 12, the forearms in 10, the thighs in 10, the axillas in 5, the back in 4, the face in 4, the scapulas in 3, the buttocks in 3, the legs in 3 and the groin in 1. Szaboky [19] found the herald plaque under the left clavicle in 77 per cent of his cases, under the right clavicle in 11 per cent, on the sacrum in 6 per cent and on one thigh in 6 per cent. In Maplestone's and Dey's [105] 19 cases the site of the herald plaque was an arm in 7, the abdomen in 5, the chest in 3, the back in 2, a thigh in 1 and the dorsum of the wrist in 1. Montgomery and Culver,[90] Schiller,[31b] Hissard,[12] Ochs,[12] Eller,[12] Friedman,[85] Oulmann [12] and Fox [32b] have reported cases in which the herald plaque was on the face. In Brocq's [106] case the herald plaque appeared around a gunshot wound on the thigh. Lord [53] cited a case in which the herald plaque was at the site of a vaccination. In Engman's and Kile's [107] patient, who had three attacks of pityriasis rosea, the herald plaque was twice on the left side of the neck. In Klauder's [37] case of recurrent pityriasis rosea, in the first attack the herald plaque was on the right hip and in the second it was back of the left knee. In Cabot's [108] case the herald plaque was on the right calf. Shellow [103] reported 2 cases and Montgomery and Culver,[90] 1 case in which the herald plaque was located on the glans penis. In 72 of our cases the herald patch was on the trunk in 37, an extremity in 24, the neck in 9 and the face in 2. In 1 the herald patch was on a palm, and in another, on the dorsum of one foot. We noted in many cases that the generalized eruption first appeared on an area far removed from the site of the herald patch, and in some instances secondary lesions never developed in this area. From these observations it can be assumed that the secondary lesions are not a direct extension from the herald plaque.

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105. Maplestone, P. A., and Dey, N. C.: The Treatment of Pityriasis Rosea, Indian M. Gaz. **72**:135, 1937.

106. Cited by Montgomery and Culver.[90]

107. Engman, M. F., Jr., and Kile, R. L.: Three Definite Attacks of Pityriasis Rosea in the Same Person, Arch. Dermat. & Syph. **34**:272 (Aug.) 1936.

108. A Macular Rash with Slight Adenopathy, Cabot Case 15182, New England J. Med. **200**:941, 1929.

XXIII. MULTIPLE HERALD PLAQUES

Maplestone and Dey [105] reported on 3 patients with multiple herald plaques. One patient had one on an arm and one on the chest, and in 2 patients two herald plaques appeared at the same time on the abdomen. Schiller's [31b] patient had three typical herald spots simultaneously. One in the bend of the left elbow and two on the abdomen. In a discussion of this case Wile [109] stated that this was the first time that he had seen multiple herald spots. Veiel,[69] however, observed that in several hundred cases a double or triple focus (herald plaque) was frequent. Multiple herald plaques were found in 4 (5.5 per cent) of our cases. One patient had three herald spots on a forearm; 1, a herald spot on an arm and on a leg; 1, two herald spots on the right thigh, and 1, two on the back.

XXIV. GIANT HERALD PLAQUE

Allen's [110a] patient had a gigantic herald plaque covering half the chest wall, and Greenhouse and Cornell [104] reported on a patient with a giant initial plaque on the right scapular region which was sharply outlined, the size of a small palm and composed of red raised scaly concentric rings, with areas of clearing between the rings. Milian [99] reported a case in which an annular giant herald plaque extended all around the neck like a napkin. In Montgomery's and Culver's [90] patient the herald plaque was a large ring on the right cheek, and in Jadassohn's [12] patient it was the size of a child's head. None of our patients had a herald plaque large enough to be termed "giant."

XXV. ITCHING

In the 380 cases of Weiss, Lane and Showman [15] 102 patients (26.8 per cent) had itching. This was severe in 48 patients and moderate in 54. The authors considered itching a feature of the disease. MacLeod [3] and Highman and Rulison [17] also observed that severe itching was common, but Little [4] stated the belief that it is rare. Montgomery [12] found this symptom in only 6 (15.8 per cent) of 38 cases, while in most of Savill's [8] it was severe. Five (27.7 per cent) of Thomson's and Cumings' [22] 18 patients complained of itching and 1 had actual excoriations. MacLeod [3] expressed the opinion that itching is most frequent in toxic and neurotic patients, and Sutton [55] stated that it is associated with sweating. In our study 130 (72.2 per cent) of 180 of the patients complained of itching. This was slight in 30, moderate in 37 and severe in 63. It is interesting that excoriations were never seen even in the most severely itchy eruptions.

109. In discussion on Schiller.[31]

110. In discussion on Fordyce.[58]

XXVI. PIGMENTARY CHANGES FOLLOWING PITYRIASIS ROSEA

Stillians and Benedek [30] presented the case of a Negress who had leukoderma for over sixteen months on the sites of former lesions of pityriasis rosea. Mitchell [111] said that he had seen the same condition, which had been called "pityriasis alba," on the tanned body of a white man, and he saw another white man with pigmentation following the disease. Runtová [112] reported 3 cases in which macular hyperpigmentation followed the involution of the lesions of pityriasis rosea. This occurrence has also been reported by Duhring,[40] Jamieson,[40] Whitfield [3] and Little.[4] On their last visit several of our patients showed some pigmentation on the sites of former lesions but we do not know how long this persisted.

XXVII. COMPLICATIONS

From our review of the literature and our own experience we can agree with Reuter's [102] statement, "Complications and sequelae of pityriasis rosea are practically unknown." The only report of a complication of this disease which we could find was that of Reuter's patient who four weeks after the appearance of a herald spot on the left forearm had a thrombophlebitis of the same arm, for which no other cause could be found. There was diffuse edema of the entire arm from the dorsum of the hand to the shoulder; the skin of the arm was reddish brown, and the veins were thick and tender. This condition persisted for some time after the rash had disappeared.

XXVIII. RECURRENCES

Butterworth [36] stated the belief that because the disease is uncommon the apparent immunity to pityriasis rosea may be based solely on the laws of chance. Stelwagon [2b] stated, "According to Thibierge, the disease does not recur, but this, I believe, does occasionally take place." Hazen [51] stated, "The disease rarely recurs," and Pusey [113] wrote, "Recurrence of the disease is rare, but occasionally happens." Ormsby [21] commented, "Recurrences are rare, though we have noted several such instances. Towle and others have reported recurrent cases." After reading Towle's [16b] report, we believe that his case should not be considered as one of a recurrence since the first eruption was not definitely diagnosed as pityriasis rosea. Second attacks have been

111. In discussion on Stillians and Benedek.[30]

112. Runtová, M.: Macular Hyperpigmentation Following Pityriasis Rosea, Ceská dermat. **15**:193, 1934.

113. Pusey, W. A.: The Principles and Practice of Dermatology, New York, D. Appleton and Company, 1925.

reported by Sayer,[114] Edelston,[55] Churchill,[55] McCaw,[55] Gray,[10b] Dwyer,[25] Whitfield,[3] Razen,[25] Robinson,[115] Gourvitch,[46] Feldman,[116] Montgomery and Culver,[90] Glaubersohn,[8] Shellow [103] and Kurtz and Davis.[56] Kogoj and Farkas [7] saw no recurrences in their series of cases, and Adamson,[11] Dore [3] and Pernet [3] stated that they had never seen a recurrence. Thomson and Cumings [22] in a large series of cases saw only one recurrence. Klauder [76] reported a recurrence of pityriasis rosea and stated that this was only the third one he had ever seen. Allen [40] had a patient with seven recurrences and another with three attacks, each of which occurred after a severe gastrointestinal upset from stopping the use of alcohol. Schamberg [33b] mentioned a physician who had pityriasis rosea three years in succession, and Zeisler [48] himself twice had the disease. Sherwell's [117] patient had pityriasis rosea during two successive pregnancies. Weiss, Lane and Showman [15] in 380 cases of the disease observed five recurrences. The second attack appeared six months, eight months, one year, eighteen months and five years after the first. They also saw 2 patients whose second eruption occurred twenty and twenty-five years later. Sayer [114] expressed the opinion that Weiss's, Lane's and Showman's [15] cases in which there was only six months and 8 months between attacks were probably recrudescences and not true recurrences. He reported 2 cases of true recurrences in which the second attack occurred four years and over two years, respectively, after the first. He stressed the need of distinguishing between a second attack and a flare-up of the original eruption and suggested setting a minimum of one year's time as the limit between an attack and a true recurrence. He said that the strong immunity developed prevents in a great majority of patients a recurrence of the disease. Engman and Kile [107] reported three authenticated attacks of pityriasis rosea in the same person. The intervals between attacks were four years and nine years. There were two recurrences in our series. One patient had a typical generalized pityriasis rosea which completely disappeared two weeks after she received 5 cc. of immune serum. Her second attack started four months later with a herald patch on the neck which was followed in two weeks by typical secondary lesions limited to the neck and the lower part of the face. Histologic examination of one of these

114. Sayer, A.: Recurrences of Pityriasis Rosea: Report of Two Cases, Brit. J. Dermat. **46**:181, 1934.

115. Robinson, S. S.: Recurrent Pityriasis Rosea: Report of Two Cases, Urol. & Cutan. Rev. **41**:111, 1937.

116. Feldman, S.: Pityriasis Rosea (Second Attack), Arch. Dermat. & Syph. **24**:898 (Nov.) 1931.

117. Sherwell, S.: Pityriasis Rosea, J. Cutan. Dis. **11**:495, 1893; in discussion on Fordyce.[58]

lesions showed the picture of pityriasis rosea. The second patient had a herald patch and a typical generalized eruption five years after she had had a similar eruption which was diagnosed pityriasis rosea.

XXIX. PITYRIASIS ROSEA IN CHILDREN

Pernet [3] found pityriasis rosea more frequent in children than in adults. The youngest patient reported in the literature was one of Crocker's,[6] aged 7 months. One third of his patients were children. Weiss, Lane and Showman [15] reported that 14.2 per cent of their patients were under 10 years of age and 1 was only 8 months old. Leiner [118] reported pityriasis rosea in a child at the age of 21 months; Savill's [8] patient was 11 months old; Little's,[4] 18 months; 1 of Thomson's and Cumings',[22] 21 months, and Adamson's,[11] 2 years. Lord's [53] son, aged 3, and Haas' [54] baby had typical pityriasis rosea. Finnerud's [101] patient was 5, and Saad's,[119] 10. Kogoj's and Farkas' [7] youngest patient was 9 years old. Of 153 of our patients 3.27 per cent were less than 10 years old and 22.22 per cent from 10 to 20. Our youngest patient was 5.

XXX. COEXISTENCE OF PITYRIASIS ROSEA AND SYPHILIS

Benedek [91] commented on the frequent occurrence of pityriasis rosea in persons with syphilis. Thomson and Cumings [22] quoted Wise as stating that pityriasis rosea is more common in patients who have had syphilis and especially in those receiving arsenical therapy. Two of Kogoj's and Farkas' [7] 46 patients with pityriasis rosea had syphilis. In our series pityriasis rosea developed in 2 patients with syphilis while they were receiving specific therapy and in another who had latent syphilis and a strongly positive Wassermann reaction of the blood.

XXXI. TREATMENT

Little [4] stated that the course of pityriasis rosea is so variable that it is difficult to evaluate the effects of treatment, and he is not convinced that any internal or external treatment shortens the duration. Montgomery and Culver [90] observed that symptoms were relieved and the course shortened by the treatment advocated by Jamieson of Edinburgh, which consists of hot potassium permanganate baths followed by the application of a 2 per cent salicylic acid ointment and talcum powder. Savill [8] saw patients with a severe form of the disease recover in two

118. Leiner, C.: Ein 1¾ Jahre altes Kind mit Pityriasis rosea, Mitt. de Gesellsch. f. inn. Med. u. Kinderh. **20**:25, 1921.

119. Saad, M. V.: Epithelioma sur lupus tuberculeux et pityriasis rosé de Gibert chez un enfant de 10 ans, Bull. Soc. franç. de dermat. et syph. **39**:552, 1932.

weeks after taking the baths once or twice a day at first and later applying a mild mercurial ointment. Whitfield [3] and Bolam [3] have observed that the duration is shortened by the use of a tar lotion but that the eruption and itching are made worse by sulfur salves. Pernet [3] obtained good results with the use of salicin. Gougerot [61] treated 12 patients with daily sponge baths, using 2 per cent eosin in 80 per cent alcohol. Herald plaques treated early did not enlarge, and the other lesions disappeared in fifteen to twenty days, while the lesions of pityriasis rosea treated with other methods lasted six to eight weeks. He obtained equally good results with a 6 per cent alcoholic solution of oil of bergamot. Leiner [120] used injections of milk in the treatment of the disease in children. Desquamation began four to five days after the injection, and involution of the rash began after one week.

Stillians and Benedek [30] gave a patient an intradermal injection of 0.1 cc. of Benedek's vaccine.[120a] The itching disappeared in one day and most of the rash in five days. Three days after a second injection the skin was entirely clear. Benedek also used this vaccine on a nurse with a severely itchy, extensive eruption of three days' duration. The itching disappeared and the rash became dull red and desquamated after the first injection, and the eruption entirely disappeared after the second. Gourvitch [46] treated 26 patients with intravenous injections of sodium thiosulfate, sodium salicylate by mouth and two to three subcutaneous injections of 0.5 to 1 cc. of a streptococcus vaccine. In all the patients the course was shortened, the eruption never lasting more than twelve to eighteen days. Barradah [121] reported on 2 patients treated with intravenous injections of streptococcus vaccine. One had received three injections in nine days, and his eruption disappeared four days after the last injection; and the other had had three injections and was well in 13 days. Maplestone and Dey [105] obtained from a patient a recent spot of pityriasis rosea with which they made a saline solution and of which 0.1 cc., increased by 0.1 to 0.5 cc., was injected every three to four days. Twenty-eight patients were cured in six to twenty (average, eleven and one-fifth) days with three to six injections.

Ormsby [21] stated "Phototherapy often causes the lesions to undergo involution rapidly. . . . Mild exposures to roentgen rays are followed by prompt cessation of subjective sensations and by more rapid involu-

120. Leiner, C.: Zur Behandlung der Pityriasis rosea im Kindesalter mit Milchinjektionen, Wien. med. Wchnschr. **71**:1801, 1921.

120a. This was made from an 8 per cent dextrose agar culture of Schizosaccharomyces hominis.

121. Barradah, M. K.: The Cure of Pityriasis Rosea—New Treatment, J. Egyptian M. A. **18**:766, 1935.

tion of the lesions." MacKee [122] observed, "Ultra-violet irradiation has been more efficacious than has x-ray treatment" but considered the possibility of the latter's being of value in severe and persistent conditions. He cited Auner's case in which the eruption disappeared in one week after a single exposure of 75 r of unfiltered roentgen rays. Allen [123] treated 3 patients with pityriasis rosea with roentgen rays and declared that in each case the eruption disappeared more rapidly than it would have with the use of regular topical remedies. In Blaschko's [124] case the eruption disappeared in two weeks with roentgen therapy. Hazen [51] admitted that roentgen rays cause a rapid disappearance of the lesions, but he considered it unwise to use general irradiation unless necessary. King and Hamilton [123] found that pityriasis rosea disappeared more rapidly after 150 to 225 r of roentgen rays than after any other treatment. In some cases they irradiated half of the body and found that the eruption on the treated half disappeared an average two weeks sooner than that on the untreated. Markson and Miller [125] expressed the opinion that two to three subfractional weekly doses of roentgen rays shorten the course of pityriasis rosea. Lord [53] applied half of an erythema dose of unfiltered roentgen rays to a herald plaque on his wife's skin. In seventeen days the spot completely disappeared, without leaving a trace, and there was no generalized eruption. Hazen [51] reported his results with ultraviolet irradiation: 7 patients were cured in four to five days with one treatment; 3, in eight to ten days with two treatments; 9, in twelve to fourteen days with two to three treatments; 4 in twenty days with four to five treatments; 3, in twenty-eight days with six to seven treatments, and 1, in six weeks with eight treatments. He asserted that slight erythema doses are necessary to produce results.

In an extensive review of the literature we found no mention of the therapeutic use of immune serum in pityriasis rosea.

AUTHORS' SERIES

The rarity of recurrence of pityriasis rosea suggested to us that the serum of patients who had had this disease might possess immune properties. Although there have been a great number of studies on pityriasis rosea, its cause is still unknown. We thought that if it could

122. MacKee, G. M.: X-Rays and Radium in the Treatment of the Diseases of the Skin, Philadelphia, Lea & Febiger, 1938, p. 735.

123. Cited by MacKee.[122]

124. Blaschko, A.: Zur Röntgenbehandlung der Hautkrankheiten, Verhandl. d. Berl. med. Gesellsch. (1908) (pt. 2) **39**:39, 1909; abstracted, Arch. Roentgen Ray **14**:129, 1909.

125. Markson, S. M., and Miller, H. L.: Pityriasis Rosea, Wisconsin M. J. **35**:875, 1936.

be demonstrated that convalescent pityriasis rosea serum has immune properties, an important step would be made toward finding the cause of this disease.

We were able to follow the results of treatment in only 114 of our 219 patients. They were divided into three groups: Fifty had received generalized ultraviolet irradiation with a quartz mercury vapor glow lamp; 38, convalescent pityriasis rosea serum, and 26 controls, only soothing applications. When indicated, patients in all three groups had been treated symptomatically, as we found that if no attempts were made to allay the troublesome symptoms the patients would not return. The treatment consisted of the application of antipruritic lotions and creams and a bland oil or cream for extreme dryness, starch baths and the administration of phenobarbital when itching caused insomnia.

The chief factor which determined the grouping of the patients was the supply of serum, which was always relatively scarce, owing to the difficulty of persuading patients to return to the clinic after they were well, in order for us to obtain their blood for use in other patients. It was also usually impossible to obtain more than 20 to 35 cc. from any one donor. Patients who on their first visit had had a generalized eruption for one week or less were given serum whenever it was available. Those whose eruption had been present longer received serum only when there was an excess supply. We preferred treating the disease in its early stages in order to eliminate the factor of spontaneous involution. The remaining patients were either treated with ultraviolet irradiation from a quartz mercury vapor glow lamp or used as controls. Patients with severe eruptions were treated with ultraviolet rays because we thought that they might not return unless given intensive treatment.

Fifty patients were given one to eight treatments with ultraviolet rays from a quartz mercury vapor glow lamp at intervals of one to three times a week. For the first treatment we gave a dose which we expected would produce a mild erythema. From the effect of this treatment the erythema dose for each person was determined and was given thereafter. Most of the exposures were followed by desquamation, which frequently caused the itching to become worse because of the associated dryness. We were surprised to note that in our series the ultraviolet irradiation did not shorten the total duration. This form of therapy, however, had an immediate beneficial effect, as after even one or two treatments the patches became much drier and paler and seemed to peel off. We found that ultraviolet rays from a quartz mercury vapor glow lamp were more effective than other forms of radiation. The lesions desquamated profusely, even when there was no scaling of the surrounding normal skin. This often gave the patches the appearance of having been scraped off with a knife.

Thirty-eight patients received serum. Blood was obtained from patients from all three groups on the day on which they were discharged as cured. The clot was allowed to retract and the serum was drawn off and placed in the ice box until needed. In every case a Wassermann test was performed at the time the blood to be used for serum was drawn. When the supply permitted, 5 cc. was injected intramuscularly once, and occasionally twice, a week. Only 1 patient was given more than three injections. The patients who received serum soon became more comfortable; many stated emphatically that the itching ceased shortly after one injection. This subjective improvement may have been suggested by the method of treatment.

We did not know to what, if any, extent the immune properties of the serum would deteriorate on standing in the ice box, but we found that the effectiveness of the serum, as measured by the duration of the eruption on the patient to whom it was administered, was not related to the length of time which elapsed between the drawing and the use of the serum. There were no serums which proved especially potent, and the effect of the same serum varied in different recipients. We frequently discovered that after the same serum was given to 2 patients, the eruption disappeared rapidly in 1 and slowly in the other. As can be seen in table 1, "second generation serum" (serum from patients who themselves had received serum) was no more effective than that obtained from patients in the other two groups. Neither the duration of the eruption before treatment nor the duration, type or severity of the donor's eruption appeared to affect the results.

Patients in the control group received only mild antipruritic topical remedies. In some patients it became increasingly difficult, the longer the duration of the eruption, to maintain their confidence. We therefore found it necessary to vary the applications from time to time.

We calculated the duration of the illness as the interval between the onset of the generalized eruption and the date of cure. The data on the time of appearance of the herald patch was too unreliable to use. The criteria for cure were the absence of new lesions; the fading, flattening and softening of the old lesions, and the disappearance of itching.

The duration of the eruption, both from the onset to the cure and from the first treatment to the cure, was slightly shorter in the group treated with serum (three and nine-tenths weeks and two and one-half weeks), and slightly longer in a group treated with ultraviolet rays from a quartz mercury vapor glow lamp (five and three-tenths weeks and three and one-tenth weeks), than in the controls (four and seven-tenths weeks and three and one-fifth weeks). We do not claim that we have demonstrated immune properties in the convalescent serum, but we do believe that it is unjustifiable to conclude that the serum has no value until it has been used in a greater number of patients, in larger doses, at shorter

intervals and in subcutaneous and intracutaneous injections. Our equivocal results may have been due to insufficient quantities of serum, too few or infrequent injections or an inadequate method of adminis-

TABLE 1.—*Analysis of Factors in Group Treated with Serum* *

Patient's Number	Duration in Weeks from Beginning of Treatment Until Cure	Total Duration of Eruption in Weeks	Duration in Weeks of Eruption at Time Treatment Was Begun	Origin of Serums Administered (Number is That of Donor)	"Second Generation Serum" (Serum from Patients Who Had Been Given Serum)	Interval Between Time Serum Was Obtained and Administered in Weeks
11	0.6	2.6	2.0	4	..	1.1
36	0.6	1.0	0.4	27	27	1.1
20	1.0	6.0	5.0	12 and 7 mixed	...	4.4, 2.4
85	1.4	2.4	1.0	80	...	1.3
10	1.5	3.5	2.0	2, 4	...	0.4, 1.0
26	1.5	5.5	4.0	8	...	5.4
171	1.5	3.0	1.5	160	...	0.7
50	1.7	2.7	1.0	43	43	1.5
24	2.0	3.0	1.0	10, 11, 15 mixed	10, 11	6.3, 2.4, 4.3
43	2.0	3.0	1.0	42	...	0.3
76	2.0	3.0	1.0	66	...	3.0
104	2.0	3.0	1.0	93, 88, 91	...	0.7, 1.0, 0.8
107	2.0	3.4	1.4	87, 91	...	0.8, 1.4
121	2.0	3.0	1.0	114	...	0.7
126	2.0	7.9	5.9	?	...	?
127	2.0	2.3	0.3	118	...	5.3
154	2.0	3.0	1.0	126	126	2.0
162	2.0	3.0	1.0	141	...	1.4
27	2.2	2.6	0.4	K,† K,† 25, 26	...	0.0, 0.0, 0.7, 5.8
138	2.3	4.3	2.0	127	127	3.4
129	2.4	3.0	0.6	125	...	4.0
115	2.4	2.5	0.1	94, 103, 109	...	8.4, 4.7, 4.4
130	2.5	3.3	0.8	122	...	9.3
158	2.5	3.7	1.2	124	...	?
110	2.6	3.0	0.4	100, 100, 93	100	1.4, 2.3, 4.2
21	3.0	3.6	0.6	11	11	4.5
22	3.0	5.0	2.0	14, 11	11	5.0
39	3.0	4.0	1.0	28, 29	...	4.4, 1.8
56	3.0	4.0	1.0	44	...	12.3
100	3.0	4.4	1.4	92, 90	90	1.3, 2.1
117	3.0	4.4	1.4	109, 107, 95	107	4.4, 7.7, 2.0
58	3.6	4.0	0.4	Mixed	...	?
69	4.0	5.5	1.5	?	...	?
123	4.0	5.5	1.5	117	117	2.5
164	4.0	6.4	2.4	141, 153	...	2.0, 2.3
71	4.3	5.0	0.7	59	...	1.0
90	5.0	6.0	1.0	82	...	1.0
72	7.0	8.0	1.0	54, 67, 63	...	2.0, 0.7, 0.7

Summary (Average in 19 Patients)

	Duration in Weeks from Beginning of Treatment Until Cured	Total Duration of Eruption in Weeks	Duration in Weeks of Eruption at Time Treatment Was Begun	Interval Between Time Serum Was Obtained and Administered in Weeks
Patients with shortest duration.....	1.7	3.4	1.7	2.2
Patients with longest duration.....	3.4	4.5	1.1	3.3
Patients treated with "second generation serum"	2.5	3.6	1.2	3.3

* Patients who received serum are listed in the order of duration of the eruption from the time serum was first injected until they were well.

† Whole blood obtained from a private patient.

tration. The effect of this serum should also be compared with that of ordinary whole blood and serum. We plan to continue this work and to investigate several other features of pityriasis rosea.

TABLE 2.—*Effect of Treatment with Ultraviolet Rays from a Quartz Mercury Vapor Glow Lamp and Convalescent Serum on the Duration of Pityriasis Rosea*

Cold Quartz Ultraviolet Rays			Control			Convalescent Serum		
Patient's Number	Total Duration of Eruption in Weeks	Duration After Treatment Was Begun	Patient's Number	Total Duration of Eruption in Weeks	Duration After Treatment Was Begun	Patient's Number	Total Duration of Eruption in Weeks	Duration After Treatment Was Begun
2	6.0	4.0	12	3.5	0.6	10	3.5	1.5
3	3.0	1.0	14	6.0	2.0	11	2.6	0.6
4	3.0	1.0	28	1.7	1.0	20	6.0	1.0
7	4.0	3.0	38	1.4	1.0	21	3.6	3.0
8	4.0	2.0	42	6.0	5.0	22	5.0	3.0
15	5.0	4.0	54	5.3	4.3	24	3.0	2.0
17	3.5	1.0	59	5.4	3.4	26	5.5	1.5
25	8.3	6.3	64	5.0	5.0	27	2.6	2.2
29	4.0	1.6	87	5.7	3.7	36	1.0	0.6
31	6.6	5.6	92	3.0	2.0	39	4.0	3.0
44	4.0	2.5	103	6.0	3.0	43	3.0	2.0
46	3.0	2.6	109	6.0	4.0	50	2.7	1.7
49	3.0	2.0	111	5.0	4.0	56	4.0	3.0
57	6.0	4.0	116	5.3	4.0	58	4.0	3.6
60	3.5	2.5	118	9.0	5.0	69	5.5	4.0
61	6.0	3.0	125	5.0	4.0	71†	5.0	4.3
63	7.0	4.0	129	4.9	3.9	72	8.0	7.0
66	6.0	3.0	141	1.9	1.1	76	3.0	2.0
67	4.0	2.0	153	5.1	3.1	85	2.4	1.4
68	4.6	2.6	156	3.3	2.3	90†	6.0	5.0
71*	5.0	2.3	160	5.0	3.0	100	4.4	3.0
73	4.0	2.0	161	11.0 *	10.0	104	3.0	2.0
79	7.6	5.0	165	5.6	3.6	107	3.4	2.0
80	6.0	3.0	177	3.4	2.0	110	3.0	2.6
82	6.0	3.0	192	0.6	0.3	115	2.5	2.4
88	6.0	2.0	197	2.3	0.9	117	4.4	3.0
90*	6.0	1.6				121	3.0	2.0
91	5.3	3.3	Total Number Patients	Average Duration in Weeks	Average Duration in Weeks	123	5.5	4.0
93	7.0	6.0	26	4.7	3.2	126†	7.9	2.0
94	5.3	4.7				127	2.3	2.0
95	4.7	1.7				129	3.0	2.4
96	4.0	2.5				130	3.3	2.5
97	6.0	3.5				138	4.3	2.3
114	7.0	3.0				154	3.0	2.0
122	10.0	6.0				158	3.7	2.5
124	4.0	1.4				162	3.0	2.0
126*	7.9	6.9				164	6.4	4.0
144	4.3	3.2				171	3.0	1.5
167	4.4	3.0						
175	3.6	3.0				Total Number Patients	Average Duration in Weeks	Average Duration in Weeks
179	6.0	2.6				38	3.9	2.5
185	6.0	3.6						
186	12.1	3.1						
190	10.4	5.3						
191	4.3	2.3						
193	6.1	4.1						
195	4.4	2.9						
196	3.1	2.4						
199	3.0	1.1						
204	1.9	0.9						
Total Number Patients	Average Duration in Weeks	Average Duration in Weeks						
50	5.3	3.1						

Summary

	Cold Quartz Ultraviolet Rays	Control	Convalescent Serum
Number of cases	50	26	38
Total duration, in weeks	5.3	4.7	3.9
Duration from onset of treatment	3.1	3.2	2.5

* Also received serum.
† Also received ultraviolet radiation.

ABSTRACT OF DISCUSSION

DR. CARROLL S. WRIGHT, Philadelphia: I have been particularly interested in the question of lesions of the mucous membranes in connection with pityriasis rosea. Two and a half years ago Dr. Guequierre, working in my clinic, showed me a lesion on the mucous membrane of a patient with pityriasis rosea. It was an oval lesion on the buccal mucosa on the right side and appeared slightly plaquelike, annular in contour and somewhat suggestive of the type of lesion that one sees on the skin. I suggested that he bring the patient to the meeting of the Philadelphia Dermatological Society, and the case has since been recorded in the transactions of that meeting (ARCH. DERMAT. & SYPH. **33**:262 [Aug.] 1938). At this time Dr. Guequierre began to pay particular attention to such lesions in patients with pityriasis rosea. I believe he has been able to find at least one such lesion in every 10 or 12 cases. There is nothing in the literature on the subject and practically no reference in any textbook except in George Clinton Anders' text on Diseases of the Skin (Philadelphia, W. B. Saunders Company). I feel that lesions on the mucous membrane can be easily overlooked. Sometimes one cannot find any, but that does not necessarily mean that there are none. It is strange that our experience should so distinctly disagree with that of Dr. Niles. The lesion on the mucous membrane has usually disappeared at the same time that the lesions disappeared from the body in the cases that I have followed to the end of the disease.

DR. JACOB HYAMS SWARTZ, Boston: I want to report more than 1 case of pityriasis rosea in my own home. Two weeks ago Mrs. Swartz became ill with pityriasis rosea, and one week later, the maid; and just before I left our child showed what might be a herald plaque. The three of them had a severe streptococcic infection of the throat about four weeks ago. I was the only one to escape the streptococcic infection, and so far I am the only one to escape the pityriasis rosea. It is interesting to note, moreover, that submaxillary adenitis preceded and accompanied the pityriasis rosea in the case of Mrs. Swartz.

DR. RICHARD S. WEISS, St. Louis: In most of the statistical part of his work, Dr. Niles has agreed with the observations in the study that Lane, Showman and I had made in 1926 (ARCH. DERMAT. & SYPH. **15**:304 [March] 1927). There is however, one point in which he differed, and I think correctly so, and that is that he found the herald patch in a much larger percentage of cases. Since 1926 my co-workers and I have been searching for the patch with greater care and have found it in a higher percentage of cases. His figure is 52 per cent, whereas ours was only 27 per cent.

He stated that we had reported itching as a feature of the disease. We did not quite make that statement. It was a feature of the disease in 26 per cent of the cases.

I was interested in his use of serum but cannot place much dependence on it from the standpoint of causation. Dr. Niles is doubtless aware that this part of his work is incomplete because of lack of controls. It is uncertain whether or not he would have secured the same result by injecting a foreign protein that does not produce a very severe reaction, which could be used as a control to see whether or not the reduction in the duration of the disease is actual and not due to foreign protein reaction. I think too that he did not employ this serum with the expectation of curing pityriasis rosea, because all physicians know that the condition clears up no matter what one does. If the patients are given relief, in the course of one or two months at most by far the greater percentage get well. I assume that Dr. Niles wanted to get on the track of some agent present perhaps in convalescent serum that might give a clue to the cause of the disease.

DR. E. WILLIAM ABRAMOWITZ, New York: It is believed that strong topical agents should be avoided in the treatment of pityriasis rosea, because the skin

of patients with this condition is easily irritated. This statement is based on the frequent observation of sulfur dermatitis from the use of the commonplace sulfur ointments. My experience with the use of 30 per cent precipitated sulfur in petrolatum in the treatment of pityriasis rosea indicates that the cutaneous lesions disappear much earlier than usual. Moriz Oppenheim, of Vienna, stated that a strong sulfur ointment was the standard treatment for pityriasis rosea as far back as Neumann's time.

DR. PAUL E. BECHET, New York: I have had such success with the quartz mercury vapor lamp in the treatment of pityriasis rosea that I was a little surprised at the indifferent results reported by Dr. Niles. I should like to ask whether he has administered fairly severe erythema doses. My best results always followed a fairly severe reaction. Under these circumstances a cure usually followed two to four treatments.

DR. FRED WISE, New York: Approximately 3 per cent of the patients I have examined in the past few years have had cervical and axillary adenopathy, an observation mentioned in connection with pityriasis rosea in most textbooks.

DR. HENRY NILES, New York: In reply to Dr. Wright, as I reported, we did not find any lesions on the mucous membranes. We thought at first that their apparent rarity was because they were not looked for, but we looked and still could not find them. We began examining the mouths of the patients with pityriasis rosea after we had started reviewing the literature and saw Dr. Guequierre's report.

In respect to Dr. Swartz's remarks, there are at least three or four reports in the literature on the relation of streptococcus infection to pityriasis rosea, and series are reported in which as high as 80 to 90 per cent of patients with this disease have given positive reactions to streptococcus vaccine, but only 15 per cent reacted to staphylococcus vaccine, and 95 per cent of the control cases gave a negative reaction to streptococcus vaccine. There are also reported cases of pityriasis rosea associated with proved streptococcus infection, such as bullous impetigo and erysipelas.

In answer to Dr. Weiss's remark regarding controls, I know we had only 26 controls. It was difficult to keep patients as controls because they would not continue coming to the clinic unless something was done for them. That is the reason why we had more patients (50) treated by ultraviolet radiation, as we often ran short of serum and could not persuade them to come in and be just controls. We are going to treat a much larger series, and we may have some more conclusive results. As Dr. Weiss mentioned, we did not do this work in an attempt to cure a self-limited disease, but to get some idea as to the causation.

In answer to Dr. Bechet, I am more surprised at the failure of ultraviolet radiation in this disease than at anything else we found. My previous experience with this treatment had been the same as his. The only explanation is perhaps that our criteria for judging complete cure were too rigid: complete absence of itching, no new lesions and flattening, paling and loss of infiltration of the old lesions. Ultraviolet radiation, as a method of cure, is not of such great value under these rigid tests. We can obtain 75 to 80 per cent improvement with two or three such treatments, but not that last 20 to 25 per cent, so that we can say the patient is 100 per cent cured by the ultraviolet rays.

In regard to Dr. Wise's question about adenitis, we looked for this in at least half our cases, but found it in very few. Dr. Hazen has commented on the frequent involvement of the lymph nodes, particularly the cervical. Generalized adenopathy has also been described. I admit that our results with immune serum are inconclusive at present.

LESIONS OF THE ORAL CAVITY CAUSED BY PHYSICAL AND BY PHYSICOCHEMICAL FACTORS

EVERETT S. LAIN, M.D.
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The oral mucosa together with the epithelium of the tongue and teeth is closely related genetically, anatomically and sympathetically to the cutaneous covering of the human body. The mouth also constitutes the beginning of the alimentary canal; hence the primitive physician learned by experience the value of routine inspection of the lingual and oral mucosa, and from such examinations he attempted to diagnose many ailments of the internal organs. Physicians today have become fairly alert to localized infections and systemic disorders which may first appear or be reflected in the oral mucosa. Early dental teaching placed much emphasis on mechanical skill in dental reconstructions, but not until recent years have physicians and dentists fully appreciated the etiologic importance of allergic, physical or physicochemical factors in lesions of the mouth. This is my reason for presenting an investigation of the subject.

It is remarkable how well the structures of the mouth are able to withstand almost continuous injury. This is doubtless because the oral cavity is composed of resistant stratified epithelium capable of rapid restoration and continually lubricated with a copious flow of mucous and salivary secretion. The submucosa is abundantly supplied with small blood and lymph vessels.

EXAMINATION OF THE ORAL CAVITY

A satisfactory examination of the oral cavity consists of more than a glance at the protruded tongue or into the mouth without the aid of a diagnostic light. The physician must be able to observe and interpret certain abnormal findings and to differentiate between those which are obviously systemic and those which appear to be due to local causes. He should remove any detachable dentures and inspect every area of the mouth, especially the buccal surfaces, the inner surfaces of the lips, the gums and the soft and the hard palate and the tongue from tip to base, using a laryngeal mirror if necessary. If lesions are found, he

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should first look for any irregular, serrated, broken or decayed teeth or metallic or other dental restorative materials which might be primary or contributory causative factors.

LESIONS DUE TO PHYSICAL OR PHYSICOCHEMICAL FACTORS

Lesions of the oral cavity due to physical or physicochemical factors may be classified as follows:

1. Physical (traumatic): localized lesions, such as erosions, ulcers, papillomas, hematomas, fibromas, granulomas, verrucae and cysts and other lesions, such as leukoplakia and cancer, in which chronic irritation is generally accepted as a contributing or predisposing factor.

2. Mechanophysical: lesions due to abnormal or distorted development of the grinding teeth or unbalanced, maloccluded artificial dentures which may cause certain reflex symptoms of the tongue.

3. Chemical: lesions due to (*a*) thermochemical causes, acute burns from hot liquids, cauterizing chemicals or tobacco and (*b*) allergic causes; reactions to certain dentifrices or toxic materials used in restorative dental work.

4. Electrogalvanic: discolorations of tissues or metals; erosions and ulcers caused by the difference of electropotentialities of the heterogeneous metals used in various types of dental reconstruction with the subsequent deposition of metals in the tissue.

1. *Lesions Due to Physical (Traumatic Factors).*—Since the advent of instruction in dental hygiene in the public schools, with its emphasis on the use of the hard or stiff brush, I have observed erosions or ulcers occurring on the gingivae and on the margins of the tongue. These traumatic lesions are most often found on the floor of the mouth and are probably due to overzealous use of the unsterile toothbrush. In contrast with this industrious habit, physicians and dentists are often confronted with evidence of gross neglect of oral hygiene by the aged or the illiterate, such as carious, serrated, broken teeth, overhanging, rough crowns or bridges or ill-fitting artificial dentures.

Prinz and Greenbaum [1] have emphasized the fact that every artificial denture is at best a foreign body and a potential source of mechanical irritation through its interference with certain physiologic functions. A few weeks after the installation of dental plates, changes in the mouth may begin to take place of which the patient is unaware. In the average clinic, routine examination of the mouth will reveal many instances of progressive shrinkage of the gingival tissue and atrophy of the maxillary processes, leaving loose, noncoapting dentures which have become sources of chronic irritation. Lesions from such

1. Prinz, H., and Greenbaum, S. S.: Diseases of the Mouth and Their Treatment, Philadelphia, Lea & Febiger, 1935, p. 213.

a cause may become so large and painful as to interfere with mastication before the patient consults a dentist or a physician.

Sutton,[2] Greenbaum and others have called attention to a certain type of granulomatous lesion occurring in the sulcus of the superior labial alveolar fold, which Sutton has named granuloma fissuratum. I have observed several such lesions both at the superior and the inferior labial fold. They are usually caused by trauma from a wing of ill-fitting dentures.

The tongue suffers equally with other structures of the oral cavity from accidental biting or from hot or chemically irritating fluids, and it may become inflamed and edematous after excessive use of tobacco and alcohol. It may undergo dorsal dekeratinization from rough or chemically irritating dentures. It often reflects the color of the denture and is spoken of as a bald or a varnished tongue. In such cases chemical examination of the blood or other laboratory analyses may become necessary to determine whether the cause is organic or local.

Convoluted Tongue, or Scrotal Tongue: This is a congenital and usually hereditary anomaly and may be unrecognized until persistent accumulations of food and debris in the furrows cause almost constant irritation. It then becomes a source of much physical discomfort and mental anxiety and requires intelligent hygienic treatment and reassuring advice from a physician or a dentist.

Serrated Tongue: During sleep or when the mouth is closed and the teeth are occluded the tongue fits snugly into the floor of the mouth between the wings of the mandibles. The margins of the tongue are drawn by suction firmly into the occlusal lines and other interspaces of the teeth. Should there be missing teeth, irregular, distorted teeth or malocclusion, the tongue after many months or years in such a periodically strained position may show indentations or projecting notched margins corresponding to the interspaces of the teeth. The labial or buccal mucosa may become molded by the same process into projecting or overlapping folds which are easily traumatized during mastication.

Hyperplasia of Circumvallate Papillae (Lingual Tonsils): Certain persons have a predisposition to hyperplasia of all lymphoid structures. A fairly common condition, second only to glossopyrosis as a cause of anxiety, is hyperplasia with a burning sensation of the circumvallate papillae, or lingual tonsils, distributed over the base and posterior margins of the tongue. Textbook descriptions of pathologic processes of the lingual tonsils are extremely brief, and discussions in the literature are rare. The great majority of the patients are hypersensitive women

2. Sutton, R. L., Jr.: (*a*) A Fissured Granulomatous Lesion of the Upper Labio-Alveolar Fold, Arch. Dermat. & Syph. **26**:425 (Sept.) 1932; (*b*) Granuloma Fissuratum, ibid. **26**:865 (Nov.) 1932.

or neurotic men, doubtless because, as was suggested by Miller,[3] emotional stress is conducive to engorgement of the various plexuses at the base of the tongue. While the patient is usually conscious only of a single lesion on one side or on the dorsum of the tongue, this papillary enlargement is often bilateral. Many causes have been suggested. I agree with others that local irritation from certain foods and drinks, accumulation of debris and infection in the open crypts of the papillae constitute the cause in most cases. I am convinced that overanxiety and frequent examinations by both patient and physician are the principal contributing etiologic factors in more than 50 per cent of all such cases. It must not be forgotten that the lingual tonsils are common primary locations of cancer. In every case careful examination should be made, together with histologic examination if the latter is indicated.

Papillomas (Granulomas): Without histologic examination fibrous papillomas of the mouth are not easily differentiated from verrucae. Careful inspection reveals that fibromas usually arise from a portion of the buccal or lingual mucosa which has been drawn by suction into some abnormal dental interspace or dental reconstruction during sleep or when the mouth is closed. Such a tumor often becomes as large as an English pea before the patient's attention is drawn to it by biting or by some other injury.

Pyogenic granulomas often arise at the gingivodental junction, although they may occur on the tongue or in any part of the buccal mucosa where a slight traumatic erosion and secondary pyogenic infection have occurred. They may be caused by piercing bristles of an unsterile toothbrush, or toothpicks or by neglect of dental hygiene which has permitted deposition of calcareous material on the peridental structure below the gingival margins. Erroneous (histologic) reports of malignant disease are occasionally made unless there is also a clear roentgenogram of the tooth.

Verrucae: Verrucae of the mouth are easily recognized, although their surfaces appear moist instead of dry like those of verrucae on the cutaneous surface. Approximately all forms of true verrucae may be due to the same virus and may differ only by reason of environment. They are infectious and autoinoculable in susceptible persons and may occur wherever superficial epithelial tissue is found. They may be present on the lips, the gingivae and the buccal mucosa, although the most frequent site is on the anterior margins or the dorsum of the tongue, a region corresponding to a point of irritation from an irregular, serrated tooth or rough dental reconstruction. Bloodgood and others have called attention to the fact that owing to constant irritation

3. Miller, M. V.: The Lingual Tonsil, Laryngoscope **40**:117 (Feb.) 1930.

warts in the mouth may after a time undergo malignant degeneration and for that reason should always be removed.

Cysts: Cysts of the oral cavity are the result of localized irritation and obstruction. Trauma with subsequent infection originating at the mouths of the ducts and solidifying chemical changes in the secretion of the ducts are the most common etiologic factors. The cysts in most cases can be recognized without difficulty. They gradually increase in size until they rupture spontaneously or become so painful that the patient seeks the advice of a surgeon. In the beginning they are benign and usually sterile, but if they become infected an abscess may result. Malignant disease may follow frequent recurrence or unsuccessful treatment.

Leukokeratosis (Leukoplakia): In the absence of some associated eruption, such as lichen planus, lupus erythematosus or certain fungous processes sometimes found on the oral mucosa, leukoplakia is not difficult to diagnose. Patches may be present on any part of the oral mucosa; my case histories reveal that they most frequently occur first on the mucocutaneous areas of the lips and may extend back from the commissures of the mouth and buccal mucosa even to the hard palate. I have not found the tongue so commonly involved except in cases of proved syphilis. It is generally accepted that the chief etiologic factor in leukoplakia is chronic irritation; the irritating factors may be traumatic, thermal, physicochemical or electrogalvanic. Histologically senile keratosis of the skin and leukoplakia of the oral mucosa are essentially the same.

Hazen and Eichenlaub,[4] Fox,[5] and Eichenlaub[6] have reported clinical and statistical reviews of several hundred cases. Fox[5] and Eichenlaub[6] called attention to the comparative infrequency of leukoplakia and cancer of the mouth in the colored races. My own investigations a few years ago among the full-blooded Indians of Oklahoma disclosed 1 case of cancer of the lip beginning with leukoplakia and not a single case of cancer of the mouth, although the Indian is an incessant smoker when economic conditions permit. In spite of the outdoor life and exposure to sunlight, there was not a single case of senile keratosis.

The records of the Lain-Eastland Clinic disclose that leukoplakia, like senile keratoses, appears most often in persons of fair complexion who have not a normal amount of cutaneous pigment. I suggest that chronic irritation, as in cancer, plays only a secondary role in the precipi-

4. Hazen, H. H., and Eichenlaub, F. J.: Leukoplakia Buccalis, J. A. M. A. **79**:1487 (Oct. 28) 1922.

5. Fox, H.: Some Diseases of the Oral Mucosa, Pennsylvania M. J. **38**:465 (April) 1935.

6. Eichenlaub, F. J.: Leukoplakia Buccalis, Arch. Dermat. & Syph. **37**:590 (April) 1938.

tation and localization of leukoplakia on the mucosa of those who, by heredity or otherwise, are predisposed to hyperkeratinization of epithelial tissue.

I have recently reviewed a series of 178 cases of leukoplakia of the oral mucosa taken from my private case records, with special reference to smoking, wearing of artificial dentures and character of the skin (whether blond or brunet). Ninety-six cases in which such factors were not particularly noted were eliminated. Seventy-seven of the patients in the remaining 82 cases were men, and 5 were women. Seventy-three of the men were smokers; 14 of these wore artificial dentures. Four were nonsmokers; all wore partial or full artificial dentures. Of the 64 men who had fair complexions, 61 showed signs of either superficial or deep senile keratosis on the hands or the face or both. One man, a full-blooded Indian who had leukoplakia of the lower lip which subsequently became a cancer, did not have any senile keratosis. Of the 5 women who had leukoplakia of the mouth, 3 admitted smoking and 4 wore partial or full artificial dentures. Four of the women had fair complexions, and 2 of these had superficial keratosis on the face and hands. One was an Indian woman who smoked and had cancer of the lower lip which had been preceded by leukoplakia; she showed no evidence of senile keratosis.

Cancer: The clinical symptoms of cancer within the oral cavity are so well known to most physicians and the general subject of cancer so large that only brief mention will be permitted in this paper. It is generally accepted that the primary precipitating factor in cancer of the mouth is chronic irritation. The presence of rough, carious or irregular teeth, crude, ill-fitting partial or full artificial dentures, chronic ulcers due to excessive use of tobacco or the warning flag of leukoplakia always demand a careful examination and perhaps a histologic examination. The responsibility resting on both the physician and the dentist to be keenly alert for all such predisposing factors in the mouths of adults cannot be overemphasized.

2. *Lesions Due to Mechanophysical Factors.*—Glossopyrosis: The complex problem of glossopyrosis has been one for occasional mention in medical and dental meetings for many years. Engman [7] called attention to burning tongue and reported 11 cases; all the patients were between the ages of 35 and 65. He emphasized the overanxiety of these patients about the possibility of cancer. More recently Fox [8] has made an extensive study, with a review of the literature and a report of 14 cases. Not until recently, however, has there been a series of cooperative studies of this distressing condition by physicians and dentists. The

7. Engman, M. F.: "Burning Tongue," Arch. Dermat. & Syph. **1**:137 (Feb.) 1920.

8. Fox, H.: Burning Tongue, New York State J. Med. **35**:881 (Sept. 1) 1935.

experimental investigations of Kirk,[9] Goodfriend,[10] Costen [11] and others appear to have proved that glossopyrosis may sometimes be caused by chronic irritation of the lingual nerve from abnormal pressure of a loose, overstrained mandibular condyle on its articulation with the temporal bone. The normal articulation of the mandible with the temporal bone consists of a shallow fossa lined with thin cartilage. The inferior division of the trigeminal nerve with its subdivisions of the chordi tympani, the auriculotemporal and the lingual branch lies in close proximity to this joint. The pressure on the surface of the mandibular fossa changes with each position of the mandible during the grinding process of mastication. The degree and direction of pressure on the articular surface vary with the normal or abnormal condition of the molar teeth, which act as a fulcrum. These potent forces acting on the mandibular articulation undergo gradual though marked angular and

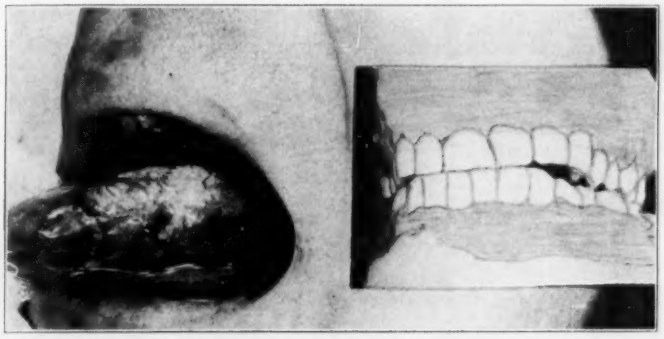

Fig. 1.—Case in which inversion and malocclusion of molars caused chronic erosion and ulceration of the tongue which eventually became malignant.

atrophic changes throughout life. After the loss of coapting molar or other grinding teeth, reconstruction of the denture should be immediately substituted, or abnormal changes in the maxillary processes and mandibular articulations will occur. Dentists admit, however, that the construction of dentures which give perfectly normal pressure balance on the mandibular joint is an ideal rarely attained.

Costen [11] has made a study of 90 patients with multiple reflex symptoms in the oral cavity from mandibular malarticulation. Eleven of

9. Kirk, E. C.: A Study of the Dynamics Involved in the Evolution of the Human Dentures in the Relation of Centric Occlusion, Dent. Cosmos **72**:631 (June) 1930.

10. Goodfriend, D. J.: Symptomatology and Treatment of Abnormalities of the Mandibular Articulation, Dent. Cosmos **75**:844 (Sept.); 947 (Oct.) 1933.

11. Costen, J. B.: Glossodynia: Reflex Irritation from the Mandibular Joint as the Principal Etiological Factor, Arch. Otolaryng. **22**:554 (Nov.) 1935.

these complained of "burning tongue," and in all instances relief was obtained by means of prosthetic restorations. During my study of oral galvanism I observed numerous cases of "burning tongue." In 2 of these the condition was completely relieved by a dentist who reconditioned the mandibular joint after correction of possible electrogalvanism had failed. I am convinced, therefore, that in addition to the known causes of glossopyrosis a local mechanophysical factor has been established.

3. *Lesions Due to Physicochemical Factors.*—Allergic Reaction to Dentures and Reconstructions: Since the discovery that skilled artisans can mold and construct a serviceable substitute for teeth, dentists and manufacturing supply laboratories have been faced with the major problem of finding a satisfactory basic denture material which would not cause the so-called rubber sore mouth. As in medicine, progress has been characterized by trial and error with many compounds of rubber known as vulcanite, to which various minerals have been added. Modern basic materials, used under various proprietary names, consist essentially of a plastic resinoid formed by a chemical combination of camphor, phenol and formaldehyde.

Discussion of this problem is relatively common in dental literature, but it is not so well known to the members of the medical profession. Within recent years Lindsay,[12] Lain,[13] Rattner[14] and others have discussed and reported cases of "denture stomatitis" in which the diagnosis was proved by patch testing. This condition is usually caused by an undercured denture which permits dissolution and absorption of certain of its chemical constituents.

Many technical procedures have been proposed for treating basic denture compounds so that their poisonous elements may be fixed and rendered inert. Dentistry has gone far toward a solution of this problem, but individual sensitivity to certain chemicals demands further research.

Sensitivity to Metals: Traub and Holmes[15] have recently reviewed the literature and reported 2 cases of stomatitis and localized dermatitis extending over the chin and portions of the upper part of the chest and caused by sensitivity to the mercury in amalgam fillings.

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12. Lindsay, H. C. L.: Traumatic Glossitis Due to Irritants Contained in Plastic Denture Materials, Urol. & Cutan. Rev. **34**:169 (March) 1930.

13. Lain, E. S.: Chemical and Electrolytic Lesions of the Mouth Caused by Artificial Dentures, Arch. Dermat. & Syph. **25**:21 (Jan.) 1932.

14. Rattner, H.: (*a*) Lesions of the Mouth from Sensitization to Base Plate Material, J. Am. Dent. A. **23**:1519 (Aug.) 1936; (*b*) Stomatitis Due to Sensitization to Dental Plates, J. A. M. A. **106**:2230 (June 27) 1936.

15. Traub, E. F., and Holmes, R. H.: Dermatitis and Stomatitis from the Mercury of Amalgam Fillings, Arch. Dermat. & Syph. **38**:349 (Sept.) 1938.

In October 1938 I observed in consultation with a dentist a case of probable silver amalgam poisoning in a girl 12 years old. She had an eruption in the mouth and on the skin similar to that in a case reported by Traub and Holmes except that in our case the dermatitis on the chin and around the mouth strikingly corresponded to the fingerprints of the dentist. The patient's mother reported a similar eruption about eighteen months previously, following the placing of an amalgam filling in another tooth by a different dentist. During my investigation of galvanism in the oral cavity I have several times observed discolored areas on the mucosa which I have attributed to sensitivity to metal rather than to galvanism.

4. *Galvanism.*—The subject of galvanism between different metallic restorations has been discussed in dental meetings at intervals for more than half a century, but a review of medical and dental literature fails to disclose a clinical study of this subject until within the last decade. At a meeting of the Section on Dermatology and Syphilology of the American Medical Association in May 1931, I [13] gave a brief report of a study made by myself and my associates of 30 cases of oral cavities containing dissimilar metallic dentures and briefly discussed symptoms and lesions which might be produced. I have since published three additional studies,[16] including a large series of case reports. The clinical and laboratory investigation which was stimulated by the publication of this work has been flattering.

Venable, Stuck and Beach [17] have since conducted a series of experiments on dogs in which they fractured the radial bones and repaired the fractures by means of metal plates and screws made from various pure and alloyed metals. They demonstrated that body fluids other than saliva contain the necessary elements of a good electrolyte. After four to six weeks the experimental animals were examined, and the chemical, histologic and roentgen findings revealed that a decided degree of electrolysis had occurred between the electropositive and the electronegative metals. In several cases there was almost total dissolution of the electropositive metals. The ionization of the dissimilar metals, though similar to that which occurs in the human oral cavity, was even more spectacular.

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16. (*a*) Lain, E. S.: Electrogalvanic Lesions of the Oral Cavity Produced by Metallic Dentures, J. A. M. A. **100**:717 (March 11) 1933; (*b*) Electric Phenomena in the Oral Cavity, Dent. Digest **40**:214 (June) 1934. (*c*) Lain, E. S., and Caughron, G. S.: Electrogalvanic Phenomena of the Oral Cavity Caused by Dissimilar Metallic Restorations, J. Am. Dent. A. **23**:1641 (Sept.) 1936.

17. Venable, C. S.; Stuck, W. G., and Beach, A.: Effects on Bone of the Presence of Metals, Based upon Electrolysis: Experimental Study, Ann. Surg. **105**:917 (June) 1937.

The data obtained by my own experiments and those of others are as follows: 1. A mouth containing two or more dissimilar metals in the presence of saliva has all the essential factors of a galvanic battery. 2. The degree of electric potential between metallic substances in the mouth depends principally on the relation of these substances to each other in the standard electromotive series of metals, although other factors may be involved. 3. Discoloration and disintegration of metallic dentures sometimes produce objective and subjective symptoms in the oral cavity.

In my series, qualitative spectroscopic examination of tissue removed from the mouth showed that in 9 of the 12 cases observed there was an abnormal content of various electropositive dental metals. In the 3

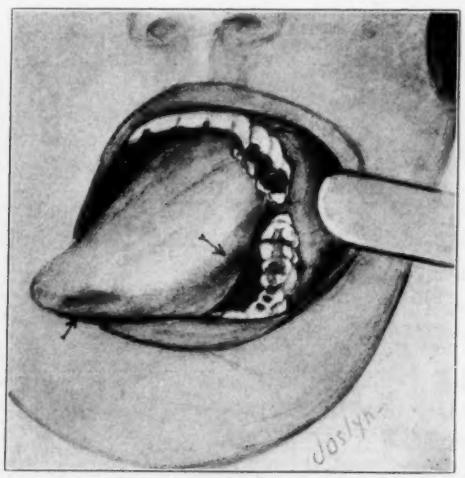

Fig. 2.—Illustration of the most commonly observed visible irritation of the tongue: caused by electrogalvanism between dissimilar metallic dentures and dental restorative materials.

remaining cases the condition was probably due to sensitivity to the metals instead of to galvanism. Lesions in the oral cavity produced by heterogeneous dental metals are not "galvanic burns." They are the tissue reaction to the localized deposition of certain ionized toxic metals.

Recent investigations by Solomon and his collaborators,[18] Miller[19] and others have consisted of electrophysical laboratory studies to determine what tissue or chemical factors constitute the necessary connecting links conducive to a flow of current. Many factors of this problem, such as the intrinsic mode of conduction, a more accurate technic of measure-

18. Solomon, H. A.; Reinhard, M. C., and Goltz, H. L.: Salivary Influence on Galvanism, Dent. Items Interest **60**:1047 (Nov.) 1938.

19. Miller, L. L.: Unpublished data.

ment and the evaluation of pathologic possibilities, remain unsolved. However, a sufficient number of case reports has now accumulated in the medical and the dental literature to confirm further my earlier conclusion that electrolysis of dental metals constitutes a pathologic entity.

SUMMARY AND CONCLUSIONS

1. The mucosa of the oral cavity is closely related genetically, histologically and sympathetically to the cutaneous structure of the human body, though it is subject to certain additional physical and physicochemical irritating factors.

2. There has not been sufficient cooperative study between physicians and dentists to differentiate systemic from local diseases of the mouth.

3. Physical, mechanophysical or electrogalvanic lesions are not infrequent. They are often attributed to local infections or systemic causes.

4. Irregular and abnormal dental development and subsequent deteriorating changes in the teeth may cause lesions of varying character and degree.

5. Many of the hypertrophies and hyperplasias caused by local physical or physicochemical factors are relatively benign, though leukoplakia and certain other lesions may become malignant and demand prompt and intelligent attention.

6. There is a close relation between racial and other inherent predisposing factors in the occurrence of leukoplakia and senile keratoses.

7. The reaction of the oral mucosa to artificial basic denture materials and metallic restorative substances has constituted a major problem which offers a further challenge for investigation.

8. Electrolysis between electropotentially dissimilar metallic dentures and dental restorative materials presents a new pathologic entity and requires further research for its complete solution.

ABSTRACT OF DISCUSSION

DR. HOWARD FOX, New York: Glossodynia, glossopyrosis and burning tongue (a term first used by Engman) are synonymous. Pain in the tongue from organic lesions due to syphilis, tuberculosis, trauma, leukoplakia, Moeller's glossitis or true neuralgia due to involvement of the fifth nerve or occasionally of the glossopharyngeal nerve should not be included under this classification. Burning tongue is not a disease sui generis but a symptom which may have many unrelated causes, including mental suggestion, pernicious anemia, with or without changes in the gastric mucosa, and probably avitaminosis. Local causes are of less importance and include the use of tobacco and the presence of jagged teeth. In my published series of 14 cases, burning tongue disappeared completely after cessation of smoking.

DR. A. J. MARKLEY, Denver: Dr. Lain has mentioned a form of stomatitis induced by dentures made of improperly cured vulcanite; this condition, known as "rubber sore mouth," rarely appears when the vulcanite is cured for twelve to

twenty-four hours but is not uncommon when the period of curing is reduced to a few hours, and particularly if colored rubber is used. Some base plate substitutes for rubber contain camphor, resinoids, formaldehyde or phenol and frequently provoke a severe stomatitis, even involving the whole mouth in cases of full dentures.

Useful information regarding such conditions may often be gained by inquiry as to recent dental replacements or reconstructions, and dentists are becoming wary of using such material instead of properly vulcanized rubber.

Dr. Arthur M. Greenwood, Boston: I should like to mention some work which Dr. Nathansen at the Huntington Clinic has been doing in the administration of estrogen in the treatment of leukoplakia. In a series of 30 cases, he obtained complete cure in 30 per cent, improvement in 30 per cent and no improvement whatsoever in the remainder. The dose used consisted of 200 to 600 units per day. With this dose, it takes one hundred and twenty days to effect a cure. The cure is not permanent, as there is recurrence in about four months. He has not yet worked out the maintenance dose.

Dr. Samuel Ayres Jr., Los Angeles: About a week ago my dentist called my attention to a condition he had observed and which appeared to indicate something new in the causation of sore mouth, namely, the solutions which patients have been using to cleanse their dentures. They immerse the dentures at night in a glass or cup containing an antiseptic and give them a perfunctory rinse before putting them into the mouth in the morning, so that the dentures often contain an appreciable amount of the antiseptic, which may be a fairly strong chemical not intended to be used undiluted. In regard to mechanical factors pertaining to lesions of the mouth, in the past year or so I have had several patients with granuloma fissuratum, the classic picture with the folded coin appearance and fissures at the bottom of them. Two of these patients were edentulous. I understand from talking to dentists that this is not uncommon in their experience. These lesions seem to occur more frequently on the upper gum and may be due to the fact that dentures do not fit closely and that friction has something to do with the beginning of the lesion. My third patient was not edentulous, but the lesion began under a bridge which permitted the accumulation of food and was somewhat loose and seemed to be a physical cause of the disease.

Dr. Dudley C. Smith, University, Va.: It is worth while mentioning that these physical and physicochemical agents may be only an exciting factor. This is illustrated by the production of bismuth or mercurial stomatitis in dirty mouths. Larger doses of these drugs can be given a patient with a clean mouth and teeth without producing stomatitis. It has been said, "A good dentist is necessary in the cure of paresis."

Mild or subclinical nutritional abnormalities, especially vitamin B complex deficiencies, may alter the threshold of irritability of the mucous membrane of the mouth to an extent that allows the production of stomatitis by mild irritants.

Dr. Henry D. Niles, New York: I should like to say a word about glossodynia. The cases of sore tongue which I have seen have practically all had a background of carcinomatophobia. On questioning the patients, one frequently obtains a history of some one in the family or among the patient's friends having died of cancer of the mouth. This is an important point. It may seem somewhat far afield, but I mentioned this finding to a psychiatrist, who agreed that the patient often associates himself or herself with a dead parent. This was particularly true in the case of an old maid whose father died of cancer of the mouth and in whom a painful tongue later developed.

Dr. Everett S. Lain, Oklahoma City: Dr. Markley has wisely emphasized the fact that even today old-fashioned vulcanite baked for twenty-four hours is the safest base material for artificial dentures. There have been a number of cases of stomatitis reported from the new plastic base material. I have already seen two such cases. It seems that the new product is not any better and perhaps not as good as old-fashioned vulcanite. Dr. Greenwood mentioned the use of estrogen in the treatment of leukoplakia. I was discussing only the mechanical causes of leukoplakia. It is my opinion that leukoplakia most frequently occurs in persons with an inherent predisposition to endocrine disturbances. Granuloma fissuratum was mentioned by Dr. Ayres. I agree with him that it is more common under the wings of the upper dentures.

ACTION OF SULFUR-CONTAINING COMPOUNDS IN ARSENICAL AND MERCURIAL POISONING

WITH REVIEW OF THE USE OF SODIUM THIOSULFATE IN DERMATOLOGIC PRACTICE AND REPORT OF EXPERIMENTS ON RABBITS WITH SODIUM THIOSULFATE, SODIUM P-SULFHYDRIL PHENYL SULFONATE AND SODIUM FORMALDEHYDE SULFOXYLATE

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One of the earliest sulfur-containing compounds to be recommended for use in combating arsphenamine reactions was a proprietary drug called "intramine" (diorthoaminothiobenzine), recommended by McDonough in 1916. According to Stokes,[1] Fraser and Duncan employed contramine, a derivative of intramine, and Greenbaum obtained good results with thiosinamine in doses of 3 grains (0.19 Gm.) in 10 cc. of water administered intravenously every one or two days. In 1920 Ravaut [2] noted that oxidation of the arsphenamines increased their toxicity in rabbits. He added sodium thiosulfate to the arsphenamine solution as a reducing agent to counteract the toxic effects of the oxidized material. He also used the drug in the treatment of arsphenamine dermatitis, which he believed might be due to the oxidized drug, and attributed the beneficial action of sodium thiosulfate to its reducing properties. He administered intravenously daily doses of 4 to 15 Gm. in a 20 per cent solution.

This work was aided by a grant from the Kuppenheimer Foundation and by a grant from Eli Lilly and Company.

From the Section on Dermatology, School of Medicine of the Division of Biological Sciences, University of Chicago.

The paper was read before the Section on Dermatology and Syphilology at the Ninetieth Annual Session of the American Medical Association at St. Louis, May 18, 1939.

1. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1934.

2. Ravaut, P.: Des traitements internes en dermatologie, Presse méd. **28**:73. 1920.

In 1923 McBride and Dennie [3a] reported beneficial results from the use of sodium thiosulfate in 7 cases of acute and chronic arsenical and mercurial complications. Immediately after publication of this report the drug came into general use for the treatment of arsphenamine dermatitis and its use was followed by a decrease in the severity and duration of this complication.

PREVIOUS CLINICAL REPORTS ON THE ACTION AND EFFICACY OF SODIUM THIOSULFATE

The beneficial effect of sodium thiosulfate was at first attributed to a supposed combination with the metallic compounds and their elimination in the form of relatively insoluble sulfides. McBride and Dennie [3a] stated in their first report that sodium thiosulfate converts the salts of arsenic, mercury, lead, bismuth, zinc and copper into the nontoxic insoluble sulfides. However, in their second report [3b] they interpreted its action as an opposite one when they stated:

> Therefore this method is based on the absolute fact that sodium thiosulphate will not only neutralize those metallic poisons which are free in the intestinal tract, but that it has the far more important action of rendering those substances soluble and excretable which have been taken up by the body and have been tightly bound by a protein radical.

This enthusiastic report was immediately challenged by Lutz,[4] who stated that an aqueous solution of sodium thiosulfate seemed to be beneficial when given intravenously to patients with exfoliative dermatitis but that in patients with acute arsenical poisoning the results were disappointing, and that he doubted its efficacy in the treatment of chronic arsenical poisoning. He attributed the enhanced efficacy of the measures for the treatment of mercurial poisoning to improvement in emergency measures adopted before absoption had taken place rather than to the action of sodium thiosulfate. He stated that the immediate injection of sodium thiosulfate into a region infiltrated with arsphenamine aggravated the condition instead of ameliorating it. Owens [5] lost no time in refuting the foregoing statement, and added: "Sodium thiosulfate is as much a specific in mercury poisoning as quinine is in malaria."

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3. (*a*) McBride, W. L., and Dennie, C. C.: Treatment of Arsphenamin Dermatitis and Certain Other Metallic Poisonings, Arch. Dermat. & Syph. **7**:63 (Jan.) 1923. (*b*) Dennie, C. C., and McBride, W. L.: Treatment of Arsphenamine Dermatitis, Mercurial Poisoning and Lead Intoxication: Further Observations, J. A. M. A. **83**:2082 (Dec. 27) 1924.

4. Lutz, H.: "Arsphenamin Dermatitis, Mercurial Poisoning and Lead Intoxication," J. A. M. A. **84**:221 (Jan. 17) 1925.

5. Owens, P. H.: "Arsphenamin Dermatitis, Mercurial Poisoning and Lead Intoxication," J. A. M. A. **84**:388 (Jan. 31) 1925.

Subsequent to the original report by McBride and Dennie,[5] many reports on the clinical use of sodium thiosulfate for patients with arsenical dermatitis and metallic poisoning appeared, which were predominantly favorable. Hoffmann [6] and Hoffmann and Schreus [7] reported good results in the treatment of arsphenamine dermatitis. Fuss and Dahlmann [8] reported favorable results in 7 patients. Deussig [9] added reports on 2 cases of severe arsphenamine eruption in which he obtained considerable benefit. Semon [10] treated 2 patients with mercurial stomatitis, 1 with bismuth stomatitis, 1 with salivation from bismuth, 1 with postarsphenamine jaundice, 1 with acute arsphenamine dermatitis, 1 with mercurial stomatitis and dermatitis and 1 with local infiltration by arsphenamine. All the patients were promptly relieved. In regard to the mechanism, however, he stated:

> The action of the salt when injected into the circulation containing a metal or an arsenical derivative is an interesting biochemical problem. I find it difficult to accept the theory that an insoluble sulfide is formed.

Kuhn and Reese [11] treated patients with postarsphenamine jaundice, polyneuritis after arsenical intoxication and acute mercurial and arsenical poisoning. The administration of sodium thiosulfate was followed by prompt improvement and a variable increase in arsenic in the urine. They interpreted the disappearance of albumin and casts from the urine as probably due to protection of the kidney by the drug.

Lehner [12] reported good results in dermatitis due to arsphenamine and mercury salicylate. He doubted the neutralization theory, since he obtained good results from the treatment of several inflammatory dermatoses in cases in which there was no question of arsenical poisoning. Kristjansen [13] reported good results from the treatment of late com-

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6. Hoffmann, E.: Zur Behandlung der Salvarsan Dermatitis mit Natrium thiosulfat, Dermat. Ztschr. **39**:299, 1923.

7. Hoffmann, E., and Schreus, H. T.: Natriumthiosulfat als Heilmittel für Salvarsan (und Hg-) Dermatitis, München. med. Wchnschr. **70**:1481, 1923.

8. Fuss, S., and Dahlmann, F.: Zur Frage der Natriumthiosulfatbehandlung bei Salvarsandermatitis, München. med. Wchnschr. **72**:345, 1925.

9. Deussig, R.: Zur Behandlung der Salvarsanvergiftung mit Natriumthiosulfat, Deutsche med. Wchnschr. **51**:1824, 1925.

10. Semon, H. C.: An Antidote for Arsenic, Bismuth, and Mercury Poisoning, Brit. M. J. **1**:662, 1924.

11. Kuhn, H. A., and Reese, H. H.: Sodium Thiosulphate in Treatment of Metallic Intoxication, J. A. M. A. **85**:1804 (Dec. 5) 1925.

12. Lehner, I.: Natriumthiosulfat in der Therapie der Hautkrankheiten, Zentralbl. f. Haut- u. Geschlechtskr. **20**:558, 1926.

13. Kristjansen, A.: Sodium Thiosulphate in Preventing Harmful Effects of Salvarsan Treatment, Ugesk. f. læger **89**:154, 1927; abstracted, Brit. M. J. **1**:93, 1927.

plications of arsphenamine therapy. Schamberg and Brown [14] reported favorable results obtained by combining thiosulfate with calcium (another drug which had been used in the treatment of complications of arsphenamine therapy) in the form of calcium thiosulfate. Marchbank, Smith and Church [15] reported recovery following ingestion of a supposedly lethal dose of mercury bichloride. They administered large doses of sodium thiosulfate by mouth in addition to that given by the intravenous route. Haag and Bond,[16] however, observed that both the oral and the intravenous administration of the drug were of no avail in poisoning by solution of potassium arsenite U. S. P. (Fowler's solution).

As is so often the case after the introduction of a new drug, the initial enthusiam has been followed by an attitude which is lukewarm if not actually skeptical. Stokes [1] stated:

> The uncertainties reflected by these laboratory conflicts have been carried over into the clinics, and while there has been no extended discussion of the matter in the literature that I have been able to find, a number of observers are less convinced of the absolute effectiveness of sodium thiosulphate, orally or intravenously, than they were some years ago. I have, for example, been repeatedly impressed with what I thought was actual damage by injections of sodium thiosulphate continued beyond the third to the sixth day of an arsphenamine dermatitis.

Beckman [17] said:

> I believe that most syphilologists are no longer particularly enthusiastic about the efficiency of sodium thiosulphate.

Moore [18] probably showed the highest degree of skepticism among syphilologists when he stated:

> In spite of seven years' experience with it, I have seen no evidence that the drug is of any value whatever, either in arsphenamine dermatitis or in any other type of arsenical or heavy metal intoxication.

Even though opinion has been expressed that the drug may be ineffective, the only report of an actually deleterious effect that we could

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14. Schamberg, J. F., and Brown, M. H.: Some Studies of Calcium Metabolism: Discussion of a New Therapeutic Compound, Calcium Thiosulphate, read before the Eighth International Dermatological Congress, Copenhagen, 1930.

15. Marchbank, H. E.; Smith, C. H., and Church, H. L.: Mercuric Chloride Poisoning with Recovery Following the Use of Sodium Thiosulphate, J. A. M. A. **96**:611 (Feb. 21) 1931.

16. Haag, H. B., and Bond, W. R.: Value of Sodium Thiosulphate in Poisoning from Oral Administration of Arsenic, J. A. M. A. **88**:1219 (April 16) 1927.

17. Beckman, H.: Treatment in General Practice, Philadelphia, W. B. Saunders Company, 1938.

18. Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

find in the literature is that of Frazier,[19] who administered sodium thiosulfate to 2 patients with arsphenamine dermatitis. This treatment was followed by aggravation of the cutaneous lesions and development of vesiculobullous and bullous dermatitis. In 1 patient bronchopneumonia with pleural exudate and acute hemorrhagic nephritis also developed. In commenting on this unusual reaction, Voegtlin and Dyer [20] stated that the heating of the solution of sodium thiosulfate for forty-five minutes at 45 pounds' (20.5 Kg.) pressure may have caused a decomposition of the salt. They also suggested the possibility of confusion of the drug ($Na_2S_2O_3$) with sodium hyposulfite ($Na_2S_2O_4$) which is far more toxic and more easily decomposed than is sodium thiosulfate.

PREVIOUS EXPERIMENTAL WORK

In view of the tremendous enthusiasm for the clinical use of sodium thiosulfate, surprisingly little experimental work has been done to determine its efficacy in metallic poisoning in animals.

Mercury and Lead.—Haskell, Henderson and Hamilton [21] found that sodium thiosulfate was inefficacious in mercuric chloride poisoning in dogs. Melville and Bruger [22] came to the same conclusion. Young and Taylor [23] found that sodium thiosulfate did not decrease the toxicity of mercury salicylate, succinimide or bichloride in guinea pigs but seemed to decrease the toxicity of potassium mercuritetraiodide to a slight extent. Curtis and Young [24] found that the oral administration of 0.5 Gm. of sodium thiosulfate per kilogram of body weight to guinea pigs, rabbits and rats previously poisoned by lead did not appreciably affect the excretion of lead. They decided that the slight effect was due to its alkaline reaction and not to any ability to form soluble or insoluble lead compounds.

On the other hand, Hess and Massaro [25] reported favorable results in the treatment of rabbits poisoned by mercury bichloride. In rabbits

19. Frazier, C. N.: Purpuric Vesiculobullous Dermatitis Subsequent to Injection of Sodium Thiosulfate, J. A. M. A. **88**:537 (Feb. 19) 1927.

20. Voegtlin, C., and Dyer, H. A.: Arsphenamine-Sodium Thiosulphate Treatment of Experimental Syphilis, Pub. Health Rep. **42**:1045, 1927.

21. Haskell, C. C.; Henderson, W. C., and Hamilton, J. R.: Sodium Thiosulphate in Mercurial Poisoning, J. A. M. A. **85**:1808 (Dec. 5) 1925.

22. Melville, K. I., and Bruger, M.: Concerning the Alleged Antidotal Action of Sodium Thiosulphate in Mercuric Chloride Poisoning, J. Pharmacol. & Exper. Therap. **42**:185, 1931.

23. Young, A. G., and Taylor, F. L.: Effect of Sodium Thiosulphate on Mercury Poisoning, J. Pharmacol. & Exper. Therap. **42**:185, 1931.

24. Curtis, A. C., and Young, A. G.: Studies of the Action of Sodium Thiosulphate in Metallic Intoxication: II. The Effect of Sodium Thiosulphate on the Excretion of Lead, J. Lab. & Clin. Med. **13**:628, 1928.

25. Hess, E., and Massaro, A. F.: Sodium Thiosulphate in Mercuric Chloride Poisoning, J. Urol. **14**:539, 1935.

given mercury bichloride subcutaneously and sodium thiosulfate intravenously, the blood urea was lower than in those treated with mercury bichloride alone. If 1 Gm. of sodium thiosulfate per kilogram of body weight was given, death could be prevented twenty-four hours after intoxication but not later than forty-eight hours after the mercury was given.

Inorganic Arsenicals.—Young [26] treated 6 rabbits with sodium arsenate and sodium thiosulfate, both given intravenously. He stated:

> Experimental work on rabbits would indicate that the drug has some value in preventing kidney damage in chronic intoxication, but that its value as an antidote when large amounts of arsenic have been injected is questionable.

Scaduto [27] gave arsenous acid to frogs, rabbits and dogs and found that subsequent administration of sodium thiosulfate did not change the course of the arsenical poisoning. Oppenheim and Fantl [28] gave 0.011 Gm. of arsenous acid per kilogram of body weight to white mice subcutaneously, followed by 0.4 Gm. of sodium thiosulfate per kilogram. No difference was noted in those so treated and the controls. Mice to which only sodium thiosulfate was given survived. Kuhn and Reese [11] administered sodium arsenate to a series of rabbits and to part of them gave sodium thiosulfate. The latter group showed less renal damage than the former. The changes in the liver and spleen were the same in both groups. Hesse [29] gave a large number of compounds to 20 rabbits poisoned by inorganic and organic arsenicals. In discussing the toxicity of metallic sulfides, he stated that arsenic and bismuth trisulfides are poisonous but that the trisulfides of cobalt, silver, mercury and antimony are much less so. He used sodium hyposulfite ($Na_2S_2O_4$), sodium trithionate ($Na_2S_3O_6$), sodium thiosulfate, ammonium thiosulphate, ethyl thiosulphate, rongalit (formaldehyde sulfoxylate), strontium thioacetic acid, thiolactic acid, isethionic acid, potassium xanthate, xanthoacetic acid, glucosemercaptol 2,5-dithiopiperazin, dialanylcystindianhydride, dileucincystindianhydride and synthetic glutathione. He was not able to demonstrate any protective effect from the substances given. However, he did state that if a sulfide has been shown to be relatively nontoxic, an effort should be made to

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26. Young, A. G.: Studies of the Action of Sodium Thiosulphate in Metallic Intoxication: I. The Effect of Sodium Thiosulfate on Arsenic Elimination, J. Lab. & Clin. Med. **13**:622, 1928.

27. Scaduto, P.: Il tiosolfato di sodio come antidoto dell'acido arsenicoso, Boll. Soc. ital. di biol. sper. **6**:578, 1931.

28. Oppenheim, M., and Fantl, P.: Das Natrium thiosulfat in der Behandlung von durch Arsenbindungen verursachten Hauterkrankungen, Arch. f. Dermat. u. Syph. **175**:438, 1937.

29. Hesse, E.: Die Entgiftungsmöglichkeiten der Metalle: Co, Ag, HSb and As, Arch. f. exper. Path. u. Pharmakol. **122**:354, 1927.

produce it by therapy. Kuhn and Loevenhart [30] gave approximately the minimum lethal dose of sodium arsenite to rabbits both orally and intravenously, followed by 50 to 100 mg. of sodium thiosulfate per kilogram. There seemed to be some protection by this method, and they concluded "that thiosulfate had some value in the treatment of arsenic poisoning when the dosage of the latter is approximately the minimum lethal dose, but the results were not very striking."

Organic Arsenicals.—Ullmann [31] gave organic arsenic in the form of neoarsphenamine and neo-silver arsphenamine intraperitoneally and intravenously to guinea pigs, in doses of 0.05 Gm. per kilogram of body weight. If immediately after, or within the first half hour, 0.1 Gm. of sodium thiosulfate per kilogram was given intraperitoneally or intravenously and the dose repeated every six hours, the animals survived, in contrast to the control animals which succumbed. On the other hand, Baba [32] administered intraperitoneally a lethal dose of arsphenamine to mice, preceded, accompanied or followed by one-half the lethal dose of sodium thiosulfate (about 1.9 Gm. per kilogram), and all the animals succumbed.

In studying other sulfur-containing drugs, Fujino [33] reported on the protective action of cysteine against lethal doses of arsphenamine and mercury. Voegtlin, Dyer and Leonard [34] found that the intravenous injection of reduced glutathione inhibited the toxic action of arsenoxide in rats. Feeding glutamic acid and cystine also reduced the toxicity, but cysteine was less efficacious than glutathione. They concluded that the data indicated that the SH group of glutathione may be regarded as the so-called arsenic receptor of mammalian protoplasm. In this connection, Brown and Kolmer [35] found experimentally that the therapeutic properties of sodium thiosulfate are dependent on something other than the sulfhydril content of the skin.

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30. Kuhn, H., and Loevenhart, A. S.: The Antagonism Between Sodium Thiosulphate and Arsenical Compounds, J. Pharmacol. & Exper. Therap. **25**:160, 1925.

31. Ullmann, K.: Erfahrung ueber Na-thiosulfat bei Salvarsan-schädigungen, Dermat. Wchnschr. **82**:11 and 56, 1926.

32. Baba, T.: An Experimental Study of Treating Salvarsan Intoxication, Jap. J. Dermat. & Urol. **24**:43, 1924; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **16**:106, 1925.

33. Fujino, S.: Neutralizing Action of Cystein Against Salvarsan and Mercury Intoxication, Folia pharmacol. japon. **10**:14, 1930; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **36**:479, 1931.

34. Voegtlin, C.; Dyer, H. A., and Leonard, C. S.: On the Specificity of the So-Called Arsenic Receptor in the Higher Animals, J. Pharmacol. & Exper. Therap. **25**:297, 1925.

35. Brown, H., and Kolmer, J. A.: The Relation of Arsenicals to the Glutathione Content of Animal Tissues, J. Pharmacol. & Exper. Therap. **35**:417, 1929.

INFLUENCE OF SODIUM THIOSULFATE ON THE TRYPANOCIDAL AND SPIROCHETICIDAL ACTIVITY OF ARSENICALS

If the administration of sodium thiosulfate is followed by action on an arsenical already in the body, it might be expected that the therapeutic efficacy of the arsenical might be altered thereby. Kuhn and Loevenhart [30] found that sodium thiosulfate inhibited somewhat the trypanocidal action of tryparsamide when 0.325 Gm. per kilogram of the former was injected forty-eight hours after the latter drug. An amount as small as 0.050 Gm. per kilogram showed no effect. Harrison [36] found that a mixture of neoarsphenamine and sodium thiosulfate was as effective therapeutically as the neoarsphenamine alone. Voegtlin and Dyer [20] reported that large doses of sodium thiosulfate did not decrease the trypanocidal efficiency of arsphenamine, neoarsphenamine or sulfarsphenamine and did not decrease the spirocheticidal action of sulfarsphenamine.

INFLUENCE OF SODIUM THIOSULFATE ON THE EXCRETION OF ARSENIC

An interesting and important phase of the study of arsenic poisoning is the influence of the administration of sodium thiosulfate on the excretion of arsenic. Its importance lies in the fact that increased excretion has been advanced as evidence of the beneficial action of the drug.

Increase in Arsenic Excretion.—Myers, Groehl and Metz [37] showed that patients with arsphenamine dermatitis or jaundice excrete a large amount of arsenic in the urine after each injection of sodium thiosulfate. They therefore attributed the beneficial effect in part to removal of the stored arsenic from the body. Myers and his co-workers [38] were so convinced of the efficacy of sodium thiosulfate that they reversed their line of reasoning by stating that the increased excretion of arsenic following the administration of sodium thiosulfate was evidence of the arsenical causation of the presenting dermatosis (usually some form of scleroderma). Ayres and Anderson [39] studied 49 cases of various dermatologic conditions in which arsenic was suspected of being a causative factor and in which determinations of the urinary arsenic were made by the Gutzeit method before and immediately after a single

36. Harrison, L. W.: Effect of Sodium Thiosulphate on the Therapeutic Power of Arsphenamine Compounds, Lancet **1**:1161, 1925.

37. Myers, C. N.; Groehl, M. R., and Metz, G. P.: Therapeutic Activity of Sodium Thiosulphate, Proc. Soc. Exper. Biol. & Med. **23**:97, 1925.

38. Myers, C. N.; Marples, E.; Groehl, M., and Throne, B.: The Use of Sodium Thiosulphate in Diagnostic Procedures, J. Lab. & Clin. Med. **11**:836, 1926.

39. Ayres, S., Jr., and Anderson, N. P.: Sodium Thiosulphate and the Elimination of Arsenic, J. A. M. A. **110**:886 (March 19) 1938.

injection of sodium thiosulfate (1 Gm. in 10 cc. of water). They observed that an increase in the urinary excretion of arsenic usually followed the injection of sodium thiosulfate. Kuhn and Reese [11] observed varying increases in urinary arsenic after the administration of sodium thiosulfate.

Further evidence that sodium thiosulfate increases the elimination of arsenic was claimed by Osborne,[40] who used the method of Justus as modifield by Brünauer and himself to demonstrate supposed crystals of arsenic sulfide in the tissues. A remarkable reduction in the quantity of these crystals was seen after the injection of sodium thiosulfate. Tannenholz and Muir [41] and Oppenheim and Fantl,[42] working independently, came to the conclusion that the crystals demonstrated by the method were not those of arsenic sulfide, so that considerable doubt has been cast on the evidence for the increased excretion of arsenic as demonstrated by this method.

Decrease or No Increase in Arsenic Excretion.—On the other hand, an approximately equal number of investigators have been unable to confirm the increased excretion of arsenic following the administration of sodium thiosulfate, but on the contrary most of them found an actual decrease in excretion. Kuhn and Loevenhart [30] observed that sodium thiosulfate reduced the total output of arsenic for twenty-four hour periods in animals poisoned with sodium arsenite, and, owing to diuresis, the amount in each cubic centimeter of urine was greatly reduced. Mattice and Weisman [43] demonstrated an actual decrease in urinary excretion of arsenic after the administration of sodium thiosulfate. Oppenheim and Fantl [28] studied 13 patients who had received arsenic at various times, most of them shortly before the study was made. After arsenical treatment had been discontinued, a twenty-four hour specimen of urine was examined for arsenic by the method of Gangl and Sanchez. Sodium thiosulfate was given to 9 of the patients, and another twenty-four hour specimen was examined. One patient showed an increase of 106 per cent, but the remainder showed decreases in amounts of as much as 60 per cent. The authors explained all the results by the normal daily variation in urinary arsenic and stated the belief that injection of sodium thiosulfate had no effect on the urinary excretion of arsenic.

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40. Osborne, E. D.: Microchemical Studies of Arsenic in Arsenical Dermatitis, Arch. Dermat. & Syph. **18**:37 (July) 1928.

41. Tannenholz, H., and Muir, K. B.: Methods for Microchemical Demonstration of Arsenic in Tissues, Arch. Path. **15**:789 (June) 1933.

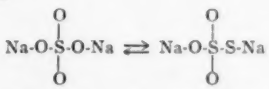
42. Oppenheim, M., and Fantl, P.: Ueber Hauterkrankungen verursacht durch arsenhaltige Wandfarben: II. Versuche zum histologischen Nachweis von Arsenverbindungen in der Haut, Arch. f. Dermat. u. Syph. **170**:488, 1934.

43. Mattice, M. R., and Weisman, D.: Urinary Excretion of Arsenic: I. Normal Subjects, Am. J. M. Sc. **193**:413, 1937.

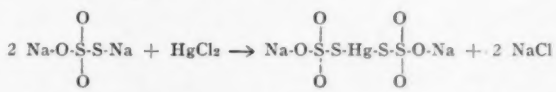
EXPERIMENTS WITH SODIUM THIOSULFATE AND SODIUM P-SULFHYDRIL PHENYL SULFONATE

In view of the conflicting results, it was decided to restudy some phases of poisoning of animals with metallic salts and the effect of various possible antidotes.

When sodium thiosulfate

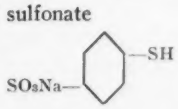


combines with metals, it probably combines in the second tautemeric form. Thus, with mercury bichloride ($HgCl_2$) it will yield

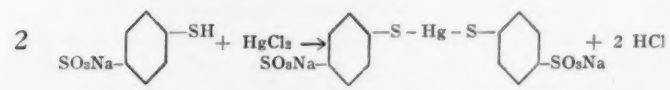


In this molecule, the mercury is little ionized, and forms a very stable bond. Most heavy metals probably combine with sodium thiosulfate in this manner.

Sodium p-sulfhydril phenyl sulfonate



will combine with heavy metals in this manner:



Inorganic Arsenical.—The work of Young [26] was repeated, with the same doses and with some modification of the doses of sodium arsenate in the various series. Sodium arsenate was given intravenously in a 10 per cent aqueous solution. The sodium thiosulfate was dissolved immediately before use, but the sodium p-sulfhydril phenyl sulfonate had been put in ampules in aqueous solution. Both were given in 5 per cent strength. Later, the sodium arsenate was used in a 5 per cent solution, so that the solutions would be of uniform concentrations.

Series 1. As controls, 4 rabbits were inoculated with 0.025 Gm. of sodium arsenate per kilogram of body weight. They lived one, four, eight and sixty days, respectively. One animal was given the same dose of sodium arsenate with 0.05 Gm. of sodium thiosulfate per kilogram and lived one day. A second animal was given 0.03 Gm. of sodium arsenate per kilogram with 0.05 Gm. of sodium thiosulfate per kilogram. The same dose of arsenic was repeated in ten and seventeen days without the thiosulfate. The animal lived sixty-three days after the first injection.

Series 2. In this series 5 control animals were given 0.025 Gm. of sodium arsenate per kilogram of body weight, followed by 0.015 or 0.025 Gm. a week later. One rabbit died in three days, but the remaining 4 survived for over fifty days. Six rabbits were given 0.025 to 0.03 Gm. of sodium arsenate per kilogram, followed by 0.015 to 0.03 Gm. at weekly intervals. Sodium p-sulfhydril phenyl sulfonate in a dose of 0.05 Gm. per kilogram was given on the same day or the

day following the first injection and the dose repeated at intervals of two weeks. Two animals survived for eleven and seventeen days, respectively, and the remaining 4 lived for over sixty days.

Series 3. Owing to the large percentage of survivors in the second series, the dose of sodium arsenate was increased in the third series. As controls, 6 rabbits were given 0.033 Gm. of sodium arsenate per kilogram of body weight, followed by 0.02 Gm. per kilogram on the following day. Four survived two days, 1 three days and 1 over sixty days after the initial injection. Five rabbits were given the same amount of sodium arsenate with 0.05 Gm. of sodium thiosulfate per kilogram on the same day or the day following the first injection, and this was repeated every week or two. Three survived two days, 1 three days and 1 over sixty days.

As controls, 4 rabbits were given 0.04 Gm. of sodium arsenate per kilogram of body weight and the same amount on the following day. Three survived one day and 1 two days. Three rabbits were given the same amount of sodium arsenate (0.04 Gm. per kilogram), followed by 0.05 Gm. of sodium thiosulfate, and they died on the following day.

Series 4. The dose of sodium arsenate was again decreased, owing to the high mortality. As controls, 8 rabbits were given 0.029 Gm. of sodium arsenate per kilogram of body weight, and six days later those that survived received 0.0175 Gm. per kilogram. Three lived one day and 1 each lived two, three, four, seven and over sixty days. Four rabbits were given 0.035 Gm. of sodium arsenate per kilogram, and this dose was repeated eleven days later for the survivors. Two lived one day, 1 two days and 1 thirteen days.

Three rabbits were given 0.029 Gm. of sodium arsenate per kilogram of body weight and 0.05 Gm. of sodium thiosulfate per kilogram on the same or following day. Two lived one day, 1 two days and 1 over sixty days. To the last animal, 0.0175 Gm. of sodium arsenate per kilogram was given every week or two, with 0.05 Gm. of sodium thiosulfate per kilogram at the same intervals for one month. Four rabbits were given 0.035 Gm. of sodium arsenate and 0.05 Gm. of sodium thiosulfate per kilogram and survived one day.

Since theoretically the maximum neutralization of the amount of sodium thiosulfate given to the animals, 0.05 Gm. per kilogram of body weight, would be for only one half to two thirds of the sodium arsenate injected, it was increased fourfold. Three rabbits were given sodium arsenate in doses of 0.04 Gm. per kilogram and immediately thereafter 0.2 Gm. per kilogram of sodium thiosulfate, the latter repeated daily for three days for the survivors. Those treated with thiosulfate died in one, two and three days, respectively. Two controls died in one day and 1 in twenty-nine days.

In these experiments it is doubtful whether any protection was afforded by either sodium thiosulfate or sodium p-sulfhydril phenyl sulfonate with the method used. Microscopic study of sections from the kidneys and livers of the animals which succumbed showed necrosis and tissue destruction, which did not vary in the animals that had received the arsenate alone and in those which had also received a sulfur compound. These findings are in contrast to those of Kuhn and Reese.[11]

Organic Arsenical.—Rabbits were given neoarsphenamine in single doses and in divided doses. As controls, 3 animals were given 0.20 Gm. per kilogram of body weight intravenously. They lived eleven, fifteen and over forty days, respectively.

Three more were given the same amount of neoarsphenamine, followed by 0.05 Gm. of sodium thiosulfate per kilogram. They lived eleven, thirteen and over forty days, respectively. Three others were given a like dose of neoarsphenamine, followed by 0.05 Gm. of sodium p-sulfhydril phenyl sulfonate per kilogram. They lived four, thirteen and over forty days, respectively.

In order to test the effect of repeated doses, 3 rabbits for control were given 0.15 Gm. of neoarsphenamine per kilogram, and the dose was repeated in nine days for the survivors. One lived three days and 2 over thirty days. Of animals receiving a like amount of neoarsphenamine along with 0.05 Gm. per kilogram of sodium thiosulfate per kilogram, 2 survived five days and 1 six days. Of those treated in the same way with sodium p-sulfhydril phenyl sulfonate, 1 lived for eleven days and 2 for over thirty days.

In view of the relatively small doses of sodium thiosulfate, the experiment was repeated with the amount increased fourfold. For control, 3 rabbits were given 0.025 Gm. of neoarsphenamine per kilogram, and the dose was repeated in six days and increased to 0.30 Gm. eight days thereafter. One lived seventeen days and 2 over thirty days. Sodium thiosulfate was given to 3 rabbits similarly treated for three days in doses of 0.20 Gm. per kilogram, and the dose was repeated once at each subsequent injection. One survived eight days and 2 twenty-three days.

EXPERIMENTS WITH SODIUM FORMALDEHYDE SULFOXYLATE

The protective power of sodium formaldehyde sulfoxylate was demonstrated by Rosenthal [44] in acute mercurial poisoning in dogs and rats in 1933. Given intravenously to rats it is protective only if administered previous to the poisoning by mercury bichloride. Dogs given mercury bichloride by mouth are protected from death if the sulfoxylate is given intravenously shortly afterward, as the absorption from the gastrointestinal tract does not occur at once and so the nephrotoxic action of the drug is delayed. However, the intravenous administration of the sulfoxylate does not eliminate the corrosive action of the mercury on the gastric mucosa, so that an oral dose of sulfoxylate is also advisable when poison has been taken by mouth. The drug is too irritating to be injected subcutaneously.

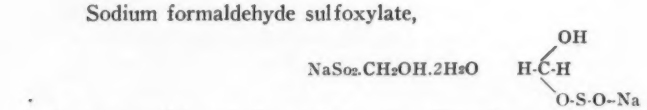
Modell and his co-workers [45] gave sodium formaldehyde sulfoxylate both intravenously and orally to cats which had been poisoned with mercury bichloride by the same route. Two thirds of the animals recovered when the sulfoxylate was given before a minimum lethal dose of mercury. It was found that the end product of reduction of mercury bichloride with sulfoxylate was toxic on injection, although less so than mercury bichloride. In the oral experiments a high degree of protection resulted if the sulfoxylate was given as soon as one to two minutes after the mercury, but no protection was evident after

44. Rosenthal, S. M.: Experimental Studies on Acute Mercurial Poisoning, Pub. Health Rep. **48**:1543, 1933.

45. Modell, W.; Gold, H.; Winthrop, G. J., and Foot, E. B.: Sodium Formaldehyde Sulfoxylate in Experimental Poisoning by Mercuric Chloride, J. Pharmacol. & Exper. Therap. **61**:66, 1937.

fifteen minutes had elapsed. The acid of the stomach content delayed the reduction process, which was accelerated by the addition of sodium bicarbonate. The product of reduction was found not to be highly toxic when given orally.

Sodium formaldehyde sulfoxylate,



is a powerful reducing agent. It will reduce mercury bichloride ($HgCl_2$) to metallic mercury.

The following experiments were carried out for the purpose of determining the protective action of sodium formaldehyde sulfoxylate in the poisoning of rabbits by mercury and arsenic.

Mercurial.—Mercury bichloride was given intravenously in a 1 per cent solution in doses of 0.025 Gm. per kilogram of body weight, which is the minimum lethal dose for rabbits. The sulfoxylate was given in a 40 per cent solution, in doses of 1 Gm. per kilogram. For control, mercury bichloride was given intravenously to 7 rabbits. Six of them died in four days (on an average), and 1 was alive at the end of two months. Seven rabbits were given the same dose of mercury bichloride which was followed in one-half to one and one-half minutes by the sodium formaldehyde sulfoxylate. Six died in three to four days, and 1 was living at the end of two months. In 7 other rabbits, the sulfoxylate was given first and the mercury bichloride five minutes later; all animals were alive at the end of two months.

Inorganic Arsenical.—As controls, 3 rabbits were given 0.04 Gm. per kilogram of sodium arsenate by the intravenous route. Two survived one day, and 1 twenty days. Three rabbits were given 1 Gm. of sodium formaldehyde sulfoxylate per kilogram, followed in five minutes by 0.04 Gm. of sodium arsenate per kilogram. All animals died on the following day.

Organic Arsenicals.—Six rabbits were given intravenously 0.20 Gm. per kilogram of a 10 per cent solution of thioarsene,[46] followed immediately by 1 Gm. of sodium formaldehyde sulfoxylate per kilogram in a 20 per cent solution. At the end of ten days 5 were dead and 1 was alive. In a second series of 6 rabbits, physiologic solution of sodium chloride was substituted for the sulfoxylate. At the end of sixteen days 3 were alive and 3 were dead. A third series of 6 rabbits, controls, were treated with thioarsene alone. At the end of thirteen days 5 were dead and 1 was alive.

In order to test the influence of sodium formaldehyde sulfoxylate when administered before the injection of an organic arsenical, 3 rabbits were given 1 Gm. per kilogram of a 20 per cent solution of sodium formaldehyde sulfoxylate, followed in five minutes by 0.20 Gm. of neoarsphenamine per kilogram. These doses were repeated in six days, and eight days thereafter the sodium formaldehyde sulfoxylate was followed by 0.3 Gm. of neoarsphenamine per kilogram. The animals died in sixteen, twenty and twenty-three days, respectively, while 1 control died in seventeen days and 2 in over thirty days.

46. Eckler, C. R., and Shonle, H. A.: A Preliminary Study of Thio-Arsene, Disodium Bis- (p-Sulfophenyl) (Acetamidophenyl) Dithio-Arsenite, Am. J. Syph. **19**:495, 1935.

RESULTS OF EXPERIMENTAL STUDIES

It is of course understood that animals do not manifest the varying degrees of hypersensitiveness to various arsenical and mercurial compounds which are seen occasionally in human beings. The rabbits which were given sodium arsenate in varying doses and at varying intervals were protected by neither sodium thiosulfate nor sodium p-sulfhydril phenyl sulfonate as given in the experiments. Any differences could be accounted for by the limits of experimental error. In the case of neoarsphenamine, the animals to which sodium thiosulfate was given lived a somewhat shorter time than those which received neoarsphenamine alone or neoarsphenamine followed by sodium p-sulfhydril phenyl sulfonate. A protective action against mercury bichloride poisoning in rabbits was demonstrated only if sodium formaldehyde sulfoxylate was given before the mercury salt. In the case of inorganic and organic arsenicals, it did not protect from poisoning by sodium arsenate or neoarsphenamine when given before the arsenical or from thioarsene when given afterward.

These findings are in conformity with most of the previous experimental work, the results of which have been largely unfavorable. The one exception is the use of sodium formaldehyde sulfoxylate before poisoning animals with mercury bichloride, for which favorable results have always been reported.

PHARMACOLOGY OF SODIUM THIOSULFATE

Since the clinical reports of the use of sodium thiosulfate have been for the most part encouraging, and since it has been assumed by many clinicians that the beneficial results are due to elimination of arsenic or other metal by the drug, it may be well to discuss the pharmacologic properties and some of the theories as to the action of sodium thiosulfate.

According to Heffter and Heubner,[47] sodium thiosulfate crystallizes with five molecules of water in large prisms. It dissolves in 1 part of water at 15 C., producing a weakly alkaline solution. It is a strong reducing agent. They stated that little pharmacologic work has been done with the drug. It is relatively nontoxic. Lasch [48] stated that it may be consumed orally without harm up to 15 Gm. per day but added that in this dose it would produce catharsis and possibly emesis. Voegtlin and Dyer [20] stated that in experiments with rabbits doses of 1 to 2 Gm. per kilogram of body weight in a 10 per cent solution,

47. Rost, E.: Schweflige Säure, in Heffter, A., and Heubner, W.: Handbuch der experimentellen Pharmakologie, Berlin, Julius Springer, 1927, vol. 3, pt. 1, p. 416.

48. Lasch, cited by Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1936.

injected slowly into an ear vein, were tolerated without the production of any symptoms. Higher doses (4 Gm. per kilogram) produced restlessness toward the end of the injection, followed by muscular weakness and depression. Baba [32] gave sodium thiosulfate to mice in doses of 2.5 to 7 Gm. per kilogram. Over 3.8 Gm. per kilogram resulted in death in four hours. The kidneys increased in volume and became hyperemic, and the vessels were dilated and hemorrhagic. When one half to two thirds of the lethal dose was given daily for one week, almost all the animals lived, though they had swollen kidneys. Nyiri [49] stated that sodium thiosulfate is partially (60 to 70 per cent) oxidized to sodium sulfate, with liberation of sulfur, and 30 to 40 per cent is excreted unchanged in the urine.

Attention has been repeatedly called to the fact that the drug should be chemically pure, and many workers have emphasized the necessity of making up a fresh solution for each intravenous injection. Voegtlin and Dyer [20] cautioned that the drug must not be autoclaved and also that sodium thiosulfate ($Na_2S_2O_3$) must not be confused with sodium hyposulphite ($Na_2S_2O_4$), which is far more toxic and more easily decomposed. Kharasch [50] stated that there should be no decomposition in well ampuled solutions of sodium thiosulfate, and several workers, among them Ayres and Anderson,[39] stated that they have experienced no difficulty with ampuled solutions.

The recommended doses for intravenous administration of the drug have not varied a great deal. McBride and Dennie [3a] recommended 0.3 Gm. on the first day, 0.45 Gm. on the second, 0.6 Gm. on the third, 0.9 Gm. on the fourth, 1.2 Gm. on the sixth and 1.8 Gm. on the eighth day. In acute poisoning from mercury bichloride taken by mouth, they gave 15 Gm. in 480 cc. of water by mouth, followed by 1 Gm. intravenously, three times daily. Most authors recommend that only a few injections be given. Stokes [1] believed that the drug should not be given for more than three to six days in arsphenamine dermatitis.

THERAPEUTIC ACTION OF SODIUM THIOSULFATE

There is no agreement as to the therapeutic action of sodium thiosulfate in complications from metallic poisoning. The various theories which have been presented, with evidence that has been advanced in their favor or against them, are:

1. *Reduction.*—Ravaut [2] first used the drug, adding it to arsphenamine for its reducing effect, in order to prevent oxidation to arsenoxide, which would increase the toxicity. He also gave the drug intravenously to reactive patients, evidently with the idea of utilizing its reducing

49. Nyiri, cited by Myers and others.[38]

50. Kharasch, M. S.: Personal communication to the authors.

action. It has since been shown that the drug would have little or no reducing action except in an acid medium, which does not exist in the body, so that it cannot act in this manner.

2. *Alkalinization.*—Curtis and Young [24] concluded that the slight increase in excretion of lead after administration of sodium thiosulfate results from the latter's alkaline reaction. The solution usually administered (10 per cent) is a neutral solution, and even a solution containing the drug in high concentration is only slightly alkaline. Shaffer [51] stated that administration of the drug should not be continued indefinitely, since it has a tendency to produce alkalosis. The manner of its action in this regard is not clear.

3. *Diuresis.*—Baba [32] stated that in mice poisoned with arsphenamine there was no neutralizing effect on the arsphenamine, but a diuretic action. Fuss and Dahlmann [8] noted an increase in the output of water both by the kidneys and the skin in patients with arsphenamine dermatitis associated with severe edema who had been given sodium thiosulfate. Kuhn and Loevenhart [30] noted diuresis after administration of sodium thiosulfate to animals poisoned by sodium arsenite.

4. *Formation of Less Toxic Metallic Sulfides.*—McBride and Dennie,[3a] who introduced sodium thiosulfate in this country, originally attributed its action to formation of sulfides which are less toxic than the original material. Considerable work has been done on this problem, and the majority of opinions is against such a conception of the drug's action as far as the interior of the body is concerned. Kuhn and Loevenhart [30] stated that sodium thiosulfate forms a less toxic compound with the metallic salts. Scaduto [27a] mixed solutions of sodium thiosulfate and arsenous acid at room temperature and at 38 C. and also boiled the mixture. Metallic sulfide was not formed even in the presence of an excess of sodium thiosulfate. It was only when the medium was made acid (p_H 4.5) that the arsenic sulfide was formed, i. e., only when nascent sulfur was released from the sodium thiosulfate. This finding would seem to justify an effort to neutralize poisons taken orally by administering sodium thiosulfate by mouth, since the content of the stomach is acid, but makes it highly improbable that arsenic sulfide would be formed in the body. It must be remembered, however, that some metallic sulfides are poisonous, while others are relatively innocuous. Meneghetti [52] found that colloidal arsenic sulfide, given by mouth, is about as toxic as arsenous acid. He stated that if arsenic sulfide is formed in the body, it would be in the colloidal form. Hesse [29]

51. Shaffer, L. W.: Treatment of Post Arsphenamine Dermatitis, Arch. Dermat. & Syph. **29**:173 (Feb.) 1934.

52. Meneghetti, cited by Scaduto.[27]

showed that arsenic and bismuth trisulfides are poisonous, but cobalt, silver, mercury and antimony sulfides are much less toxic. It would therefore seem more logical to administer sodium thiosulfate by mouth in mercurial poisoning than in arsenical poisoning, since the mercury sulfide which would be formed is relatively nontoxic compared with mercury bichloride, the substance usually ingested. As stated previously, Semon found it difficult to accept the theory that an insoluble sulfide is formed.

The predominance of negative experimental results in animals over the few positive results is against the probability of the formation of metallic sulfides in human beings. If such action takes place in man, it should take place also in animals, since their tissues have so many chemical similarities.

5. *Rendering Metallic Salts Soluble and Excretable.*—This action was emphasized in the second report of Dennie and McBride,[3b] without evidence being reported, but has not been considered by any authors since that time. The increased excretion of arsenic and mercury after administration of the drug might be used as an argument in favor. However, about 50 per cent of the reports on excretion fail to indicate any increase, so that the question must be considered as still open.

A weighty argument against direct action on the arsenic itself, as illustrated by theories 4 and 5, is advanced by Lehner,[12] who obtained as good results in nonarsenical as in arsenical dermatitis.

6. *Intravital Formation of Sulfur.*—Moore [18] called attention to the belief that has prevailed for many years that sulfur is an antidote for metallic poisoning. Nyiri [49] found that sulfur is liberated in the body from sodium thiosulfate, but Scaduto [27] expressed doubt that this occurs. Koch [53] stated that the action of sodium thiosulfate may be due to its sulfur content. Sollmann [54] stated:

> It appears to be successful against the dermatitis and the arsenical jaundice, but the evidence for the mechanism of its action is not known. . . . Since thiosulphate has a similar beneficial effect on non-arsenical and non-metallic dermatitis, it is quite conceivable that the action is not on the arsenic, but that it is perhaps an allergic response to the precipitation of colloidal sulfur.

When injected into an area infiltrated with arsphenamine, however, he believed that the effect was simply that of a diluent.

Oppenheim and Fantl [28] stated that the good results from sodium thiosulfate were due to the breaking off of sulfur in the body and that the effect had nothing to do with arsenic itself. He called attention

53. Koch, F. C.: Personal communication to the authors.

54. Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1936.

to the fact that disturbances in carbohydrate and protein metabolism are often observed in patients with arsphenamine dermatitis. The use of sulfur waters internally is said to increase the formation of glycogen in the liver. One gathers from the more recent method of treating arsphenamine complications, by means of dextrose,[51] that the action has something to do with the liver. It may well be that the result is similar to that reported for sulfur and perhaps obtained by injection of sodium thiosulfate.

Mueller and Delbanco [55] classified the injection of sodium thiosulfate as sulfur therapy but had a different explanation for its action. They stated that the point of action of the drug was unknown but its administration removed the irritability of the sympathetic nervous system, permitting resumption of normal regulation and restoration of skin tonus and function. They quoted Schuster as having demonstrated increased excretion of mercury after sulfur baths. Other physicians specializing in baths have claimed an increase in general metabolism from the same source. Mueller and Delbanco attributed arsenical dermatitis to a secondary action through the vasomotor system. As a result, the skin is not able to resist irritation, including that from arsenic in amounts which would ordinarily cause no trouble. After administration of sodium thiosulfate the function of the skin improves and arsenic is liberated.

As regards other possible methods of therapeutic action of sodium thiosulfate, Brown and Kolmer [35] found experimentally that the therapeutic properties of sodium thiosulfate are dependent on something other than the sulfhydril content of the skin.

ACTION OF SODIUM FORMALDEHYDE SULFOXYLATE

It is generally agreed that sodium formaldehyde sulfoxylate acts in vivo by its power of reducing mercury bichloride, whereby it forms a less toxic mercurial compound. Reduction also takes place in vitro, and the resulting substance has been shown [45] to be less toxic when administered to animals than the original salt.

COMMENT

From the foregoing review it is seen that a great deal of apparently contradictory evidence has been presented. It must be remembered, however, that different compounds and different animals have been used by the various investigators, and various methods of administration of sodium thiosulfate have been employed. From the data presented, it may be assumed that there is little if any evidence that sodium thiosulfate

55. Mueller, E. F., and Delbanco, E.: Zur Schwefeltherapie in der Venereologie und Dermatologie, Zentralbl. f. Haut- u. Geschlechtskr. **20**:398, 1926.

acts on arsenical or mercurial salts to form sulfides in the body, owing to the improper p_H, although the acidity of the stomach is such that a sulfide may well be formed there if the drug is given orally for poisoning by ingestion. There would be little advantage in giving sodium thiosulfate by mouth in arsenical poisoning, to substitute the relatively toxic arsenic sulfide for some other arsenical salt, but mercury sulfide is so relatively nontoxic that the administration of sodium thiosulfate by mouth should be of distinct help if made early.

According to Kharasch,[56] sodium thiosulfate, or any similar sulfur compound, should not act on an arsenical with a double bond between the two arsenic atoms, such as is present in arsphenamine. However, after arsenoxide has been formed in the body, the double bond has been broken, and such action could theoretically take place. In the body tissues, however, the p_H is not correct for sodium thiosulfate, since it combines only in an acid medium, but sulfhydril derivatives could be effective, as was shown for glutathione.[34] Our negative results with sodium p-sulfhydril phenyl sulfonate may have been due to the method of administration, whereby the drug was not present at the time arsenoxide was produced in the animal from the breaking down of neoarsphenamine. This phase of the problem suggests the possible value of glutathione or other sulfhydril compound in poisoning by an overdose of arsenoxide (mapharsen).

A valid argument could be raised that the reduction of the severity and duration of arsphenamine reactions has been so definite in many countries since the introduction of sodium thiosulfate that the drug must be responsible. There are at least two other factors of possible participation in this change. At the same meeting at which McBride and Dennie [3b] made their first presentation, Stokes and Cathcart [57] emphasized the importance of focal and intercurrent infections in the production of arsphenamine reactions. Since that time, more attention has been paid to the elimination of foci of infection previous to arsphenamine therapy, and greater care has been taken to make certain that the patient is not febrile at the time of administration of this drug. A second factor, for which there is no absolute evidence, is the possibility that manufacturers have achieved an improvement in the chemical purity of arsphenamine, resulting in fewer reactions. Against this assumption is the fact that favorable reports emanated from several countries, and it is illogical to assume that a sudden change in the drug would have occurred simultaneously over such a large territory. On the

56. Kharasch, M. S.: Personal communication to the authors.

57. Stokes, J. H., and Cathcart, E.: Contributory Factor in Post-Arsphenamin Dermatitis, with Special Reference to the Influence of Focal and Intercurrent Infection, Arch. Dermat. & Syph. **7**:14 (Jan.) 1923.

basis of an analysis of the possible mechanisms of action of sodium thiosulfate it would seem, from the evidence presented, that the most logical conception of its action is that of the intravital formation of sulfur. This suggests the advisability of further study of the sulfur problem in combating reactions from arsenic and mercury. Diuresis has been regularly reported and may also play a role.

SUMMARY

The literature is reviewed relative to the clinical and experimental evidence for the value and action of sodium thiosulfate and other sulfur-bearing compounds and sodium formaldehyde sulfoxylate in poisoning by various metallic salts, especially arsenic and mercury.

Studies carried out on 123 rabbits poisoned with inorganic and organic arsenicals and mercury failed to show any protective action of sodium thiosulfate or sodium p-sulfhydril phenyl sulfonate, as used in various ways. Microscopic examination of the kidneys of animals poisoned by sodium arsenate showed the same degree of degeneration regardless of whether sodium thiosulfate or sodium p-sulfhydril phenyl sulfonate had been given.

The pharmacology of sodium thiosulfate is presented. It is a safe drug to use in the recommended dosage.

Analysis of the possible modes of action of sodium thiosulfate—reduction, alkalinization, diuresis, formation of less toxic metallic sulfides, rendering metallic salts soluble and excretable and intravital formation of sulfur—suggests the probable action by intravital formation of sulfur, a substance which has long been used in the treatment of metallic intoxication.

Theoretically, sodium p-sulfhydril phenyl sulfonate should have a more definite action on arsenicals because of its sulfhydril group, but this was not demonstrated in the experiments performed.

Sodium formaldehyde sulfoxylate protected rabbits poisoned with mercury bichloride only when given before the latter and not when given afterward. It had no protective action against poisoning by inorganic and organic arsenicals, regardless of whether it was given before or afterward.

Sodium formaldehyde sulfoxylate acts by reducing mercury bichloride to metallic mercury, which is considerably less toxic. It protects only when given previous to the mercurial salt when the latter is administered by the intravenous route. When the mercurial salt is given by mouth the protective drug must be administered only a few minutes thereafter. If the latter is given orally for mercurial poisoning by ingestion, it should be given with sodium bicarbonate, to counteract the effect of the gastric acid, which delays reduction of mercury salts.

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ABSTRACT OF DISCUSSION

DR. CHARLES C. DENNIE, Kansas City, Mo.: In 1933 McBride and I published the first paper in this country on the use of sodium thiosulfate in the treatment of arsenical dermatitis, lead poisoning and mercury poisoning. In those days we knew nothing whatsoever of the nine day erythema of Milian, and many of the patients we treated at that time we now recognize as being of that group which would have recovered spontaneously had no treatment been given. Yet, after all these years of administering sodium thiosulfate, though its action cannot be explained chemically, I still feel that it has a place in the treatment of arsenical dermatitis. After two or three years during which we received both favorable and unfavorable criticism, we began to question the efficacy of sodium thiosulfate, so we decided to do some experimental work ourselves. We have never published the results except in one paper, "The Toxic Action of Sodium Thiosulphate." We decided to see whether sodium thiosulfate would protect dogs against the poisonous effects of mercury bichloride. Goldblatt worked with me and afterward published a paper on the treatment of mercurial poisoning with sodium thiosulfate.

We found that we should give these dogs mercury in the same way that a human being would take it, that is, by mouth. So we gave each dog 7½ grains (0.48 Gm.) of mercury bichloride in that manner. If we washed out the stomach with plain water before twelve minutes, the dog did not die; but if we left the mercury bichloride in the stomach more than twelve minutes, it did not make any difference what we did—wash out the stomach or give sodium thiosulfate intravenously or by mouth—the dog died.

We found that the greatest factor in the prevention of death from mercury bichloride was the observation of an old principle: Wash out the stomach within twelve minutes after ingestion. Goldblatt called attention to the fact that if the patient vomits immediately after taking mercury bichloride, his life is usually saved.

Then we decided to experiment on dogs by giving them mercury intravenously. It had been previously determined by Sanson that 4 mg. of mercury bichloride per kilogram given intravenously was the minimum lethal dose for a dog. None ever survived this dose.

If we gave the dogs 3 mg. per kilogram intravenously, a few would survive even though no treatment was given. So we sacrificed many dogs. We gave them the sodium thiosulfate intravenously before we gave them the mercury bichloride, 4 mg. per kilogram, and invariably the dogs died. We gave them the sodium thiosulfate at various lengths of time after the administration of bichloride of mercury, and invariably the dogs died. We gave them sodium thiosulfate by mouth and invariably the dogs died. In fact, the experiment showed that sodium thiosulfate gave no protection. It did not make any difference at what time or in what amount the drug was given.

Then we thought that perhaps the sodium thiosulfate was causing their deaths. We carried out some experiments on the toxicity of the drug and reached the point where we could give dogs 1 Gm. of sodium thiosulfate per kilogram intravenously for ten to fifteen days in succession without observing any effect on the dog with the exception of a consistently lowering of the blood sugar. We decided one thing definitely—that sodium thiosulfate in large doses was not toxic to dogs. The effect of the mercury bichloride poisoning was interesting. We made an autopsy on every dog, sectioned all the organs and found that the effect of mercury bichloride was as great on the liver as on the kidney. We were inclined to believe that the tremendous rise in nonprotein nitrogen and urea, which sometimes reached

a height of 200 mg. in each hundred cubic centimeters, was due as much to damage of the liver as to damage to the kidney.

We went so far in our experiments on dogs that we made a permanent fistula in order to drain the gallbladder after sublethal doses of mercury had been given intravenously to see if the mercury was excreted through the bile, but at that time we did not have an accurate method by which we could determine the amount of mercury in the bile.

Our experiments, which were carried on some twelve or fifteen years ago, were exactly the same as the experiments carried out by Dr. Becker.

We must grant then that certainly sodium thiosulfate is not a sure cure in any kind of heavy metal poisoning, but we have evidence to show that sodium thiosulfate has some sort of action in human beings that it does not have in animals, that protects them to some extent against arsenical poisoning.

Now, the tests for arsenic in the urine and in the blood of human beings have not been worth anything until the last five years because of the fact that chemically pure sulfuric acid contained enough arsenic that it could be recovered from the specimen. A great deal of work has been done on spinal fluid as to the excretion of arsenic, but to my mind the results are erroneous, owing to the fact that even the so-called chemically pure substance contained traces of arsenic.

We have now a sulfuric acid that is as near free of arsenic as can be, and I think that the chemical work that is going on at present is a great deal more accurate than it was before.

This has been a very nice piece of work Dr. Becker has done. He has delved into the matter again and has shown that as far as animals are concerned this drug offers no protection. But one thing must be remembered which is never mentioned in experimental work: The human body has a set of excretory organs, known as sweat glands, which the dog and the rabbit and the cat do not possess.

DR. SAMUEL GOLDBLATT, Cincinnati: I want to amplify Dr. Dennie's remarks a little. It is true that we were unable to show the slightest beneficial effect from extremely large doses of sodium thiosulfate administered to dogs that had been poisoned with mercury bichloride, given either by mouth or intravenously, if they were kept under the influence of ether or other anesthetic so that they did not vomit for more than twelve minutes. However, experiments that went on with cholecystotomies and fistulas, following Dr. Dennie's acquaintance with the work, were distinctly successful, although we were unable to measure the amount of mercury excreted. Dogs poisoned intravenously by twice the minimal lethal dose of mercury bichloride recovered and were repoisoned several times, as long as the tube leading from the gallbladder to the outside was kept open. When the tube was closed, the dog began to show all the symptoms of classic mercury bichloride poisoning.

To get back to the question of the arsenicals with reference to human beings: I have maintained for fifteen years that one of the prime reasons for bad results with sodium thiosulfate in the treatment of arsenical intoxication in patients was the small size of the dose. I have never administered to a human being a dose of less than 3 Gm. intravenously. I have given on many occasions as high as 15 Gm. intravenously. Our routine during the period that we were studying acute mercury bichloride poisoning in the wards of the Cincinnati General Hospital was to administer 10 Gm. of sodium thiosulfate four times a day.

The drug when freshly prepared from an alcohol-precipitated crystal is apparently much less toxic than ordinary salt solution. The results in acute arsenical

dermatitis and in chronic arsenical dermatitis, including the arsenical fixed eruptions, when sodium thiosulfate is given in adequate doses, are quite dramatic.

DR. S. WILLIAM BECKER, Chicago: I think one of the reasons sodium thiosulfate does not protect from metallic poisoning is that the p_H of the body is not on the acid side.

With regard to larger doses of sodium thiosulfate, it is known that they are perfectly safe. Voegtlin and his co-workers could give rabbits up to 4 Gm. per kilogram, which is a large dose, before disagreeable symptoms began. In mice, another worker could give up to 3.8 Gm. per kilogram before the drug proved fatal.

There are two phases of the investigation that this work suggests continuance of. The first is the correlation of studies on arsenic. Unfortunately, practically every worker with arsenic uses a different method for the determination of arsenic content and, as Dr. Dennie has just stated, the methods are changing and are becoming more reliable. The only way to overcome that difficulty is to take all the methods that have been used and check them against one another and see how they compare. The most logical explanation for the action of sodium thiosulfate is that of formation of sulfur in the body. Dr. Klauder has shown that in exfoliative dermatitis the sulfur in the skin is very low. Whether in the doses given it is possible to supply enough sulfur to make up that deficit, I think is questionable and may be an argument for the large doses recommended by Dr. Goldblatt.

There certainly are several things about its action that are not understood, but one must admit that there is something about sodium thiosulfate therapy that helps the patients.

PREVENTION OF INDUSTRIAL DERMATITIS

WITH REFERENCE TO PROTECTIVE HAND CREAMS, SOAP AND THE HARMFUL ROLE OF SOME CLEANSING AGENTS

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The important role of cleansing agents applied to the skin in the causation of industrial dermatitis has been stressed by a number of writers. It is worthy of emphasis that trade dermatitis is caused annually in an enormous number of cases not by the substances encountered at work but by the removal of these substances with methods harmful to the skin.[1] Soap and water constituted a contributory factor in the production of eruptions in at least 249 of Downing's [2] series of 2,000 cases of cutaneous disease arising in industry. Horner [3] remarked that he had observed more cases in which dermatitis was due to the improper use of cleansing agents than cases in which the dermatitis was due to contact in the occupation.

For the purpose of this study we questioned in detail all patients and other persons employed in industry concerning the manner in which they washed their hands: the kind of soap used, by whom it was furnished (employer or employee), the frequency of washing and the use of other cleansing agents, emollients and protective medicinal applications. In addition, we made surveys of factories and workshops in different industries, to obtain the aforementioned information and also to observe facilities provided for washing and measures other than mechanical employed in the prevention of industrial dermatitis.

Our observations emphasized measures in prevention of industrial dermatitis which other writers have stressed and which we shall not

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From the Research Institute of Cutaneous Medicine.

Read at the Sixty-Second Meeting of the American Dermatological Association, Inc., Monte-Bello, Quebec, Canada, June 3, 1939.

1. Overton, S.: Industrial Dermatoses: Their Causation, Recognition, Prevention, and Treatment, Brit. J. Dermat. **41**:255, 1929.

2. Downing, J. G.: Cutaneous Eruptions Among Industrial Workers: A Review of Two Thousand Claims for Compensation, Arch. Dermat. & Syph. **39**:12 (Jan.) 1939.

3. Horner, S. G.: Some Observations on Industrial Dermatitis, Lancet **2**: 233, 1934.

discuss. Reference is made to mechanical devices to replace manual contact, exhaust systems, closed processes, clean protective clothing, shower bath facilities, general department sanitation ("house cleaning" in the sense of the safety engineer) and hygienic practice of the worker. Such measures in the prevention of industrial dermatitis are essentially an engineering problem and are more fundamental than are the use of protective applications to the skin and the use of cleansing agents, which are concerned in this paper. These measures are especially in effect in large factories with a safety engineering department. They are frequently lacking, doubtless for financial reasons, in the smaller factory or workshop.

Not until industry is more mechanized and the worker and others concerned are better educated (in the manner later discussed) will the measures concerned in this paper become an anachronism. Our observations emphasize the need of education regarding the following important factors in the prevention of industrial dermatitis: the use and abuse of soap, the use of soap substitutes, the proper and improper use of cleansing agents other than soap, the use of emollients, the unnecessary exposure of the skin to primary irritants and to sensitizing substances, the use of a brush instead of a cloth, the use of a tool instead of the hand, the use of protective sleeves [4] and the provision of facilities and preventive means that are simple and easily provided. The industrial physician should show greater interest in what appears to be a minor consideration: the method used by employees in his plant to cleanse their hands.

Our observations cause us to marvel at the efficacy of the human skin in resisting abuse and irritation and to express surprise that there is not a greater incidence of industrial dermatitis than now prevails.

Safety engineers with whom we conferred had a proper concept of the problems involved in the prevention of industrial dermatitis. The real difficulty is the education of the worker himself and of others concerned. In this connection, Downing [5] noted a decrease of nearly 75 per cent in the incidence of industrial dermatitis in one plant after a recent lecture.

PROTECTIVE MEDICINAL APPLICATIONS

In the absence of mechanical measures of protection and when gloves are not worn, protective applications to the skin are to some degree effective. There are disadvantages to the wearing of gloves; they are usually not worn unless there is exposure to powerful cutaneous

4. We refer to the need of a greater choice of material and design than is, according to our experience, now available. We refer to the use of such articles as fingerless gloves or a glove and protective sleeve in one piece and to the use of materials for protective sleeves and gloves that are light yet durable (for instance, airplane cloth, oiled silk, cellophane and pliofilm).

5. Downing, J. G.: The Skin and Industry, Indust. Med. **1**:19, 1932.

irritants. Circumstances in which protective applications are indicated embrace different occupations, in which the work is of a dry, wet or dusty character or entails exposure to primary irritants or sensitizing substances.

The application of a simple agent, such as hydrous wool fat, glycerin, a bland oil, grease, cream or paste, or even talc, may afford some degree of protection and for this purpose have been recommended by many writers. We believe, however, that the protective action of such simple agents can be improved by the addition of other ingredients or by a combination of different agents in appropriate vehicles.

Curschmann [6] advised equal parts of zinc oxide and olive oil or of eucerin (oxycholesterol) anhydrate and glycerin. Hopf [7] recommended chinosol (potassium hydroxyquinoline sulfonate). Schultze,[8] referring to Germany, stated that there are a great number of protective creams commercially available, some of which are especially prescribed for certain industries.[9] Attempts have been made to employ preparations that "tan the living skin." Such a preparation (known as cutigen, a mixture of tannins obtained from oak bark and other vegetable matter) has been proposed by Haustein and Jäger [10] as a protective application.

Some writers recommend the use of a protective ointment, cream or paste without specifying its nature. Few formulas have been published. The following have been recommended:

By James [11]	Per Cent
Ivory soap flakes	7.48
Glycerin	26.40
Sodium silicate	24.20
Tragacanth	0.21
Oil of Lemon	0.16
Water	41.60

6. Curschmann, F.: Vorkommen, Entstehung und Verhütung beruflicher Hauterkrankungen, Arch. f. Dermat. u. Syph. **173**:222, 1935.

7. Hopf, G.: Ueber die Begutachtung von Gewerbedermatosen, Dermat. Wchnschr. **107**:1129, 1938.

8. Schultze, W.: Bisherige Arbeiten auf dem Gebiet der Hautreinigung mit Anregungen für die weitere Arbeit, Zentralbl. f. Gewerbehyg. **15**:81, 1938.

9. The foreign preparations lupocid (salicylic acid, resorcinol, carvacrol [methyl-isopropylphenol, $CH_3.C_6H_3OH.C_3H_7$], chlorocarvacrol, naphthol, bismuth and magnesium silicate in petrolatum) and borolan (yellow wax, honey, boric acid, olive oil in a petrolatum and hydrous wool fat base) were recommended as protective as well as medicinal applications. According to Finkenrath (Die Wirksamkeit einiger Schutz- und Heilmittel gegen Berufsekzeme: I. Lupucid und Borolan, Zentralbl. f. Gewerbehyg. **14**:206, 1937), these preparations are not efficacious as protective applications.

10. Haustein, F., and Jäger, R.: Die technik der Lebendgerbung, München. med. Wchnschr. **81**:143-144, 1934.

11. James, A. P. R.: An Aid in the Management of Occupational Contact Dermatitis (Dermatitis Venenata), Arch. Dermat. & Syph. **30**:30 (July) 1934.

By Fantus[12]	Per Cent
Zinc stearate	8.00
White wax	4.00
Spermaceti	12.00
Wool fat	8.00
White petrolatum	48.00
Rose water	20.00
Oil of rose	0.02

By Collis[13]		
"Mineral lard" (probably petrolatum)	3 pounds	(1.36 Kg.)
Paraffin	6 ounces	(170.1 Gm.)
Cyllin (a preparation of creolin)	3 ounces	(85.05 Gm.)

A number of preparations labeled "protective" (creams, liquids, ointments and pastes) are available commercially in this country. The exact ingredients of most of them are not known. As far as we have been able to determine, the active ingredient (the substance that leaves a film on the skin) is paraffin, wax, gum, sodium silicate or casein.

Some of the commercial preparations contain soap. We regard this as undesirable. As is later discussed, one objection to soap as a detergent is its alkalinity, which interferes with the normal acid reaction of the skin.

In our study, in which we proposed different formulas, we endeavored to fulfil certain requirements: The preparation should be sufficiently adherent so that it is not easily rubbed off, and yet it should be possible to remove it without too much difficulty at the end of the work day. Objectionable features should be lacking, such as excessive greasiness, stickiness and drying effect on the skin. The ingredients should have no, or very little, sensitizing capacity. A choice of applications of a greasy, nongreasy or waterproof character should be available, as the nature of the work demands.

In selecting ingredients, we considered the following substances that when applied to the skin leave an impervious coating or film: rubber (latex), rubber compounds (pliolite, Goodyear), synthetic rubber (neoprene, DuPont; koraseal, Goodrich), various guttas, vegetable gums, glues, resins, paraffin, yellow wax (beeswax), silicic acid and its compounds, casein, agar and cellulose and its compounds. The newer plastics employed for a variety of industrial purposes (artificial resins, such as alkyd and vinyl resins), phenol formaldehyde, urea formaldehyde

12. Fantus, B.: General Technique of Medication, ed. 3, Chicago, American Medical Association, 1938, p. 138.

13. Collis, cited by Downing.[5]

and coumarone were considered but were not employed on account of their sensitizing capability.

From this list we selected substances that were regarded as appropriate and compounded them alone or in combination in varying percentage in different bases.[14] We selected the formulas which are given in the following paragraphs and subjected them to clinical trial.

Group 1.—This group of substances comprised compounds of petrolatum or benzoinized lard, stiffened with paraffin, yellow wax, hydrogenated cottonseed oil or synthetic wax (glyceryl monostearte [14a]), to which was added one or more of the following substances: sodium silicate, latex,[15] acacia, glycerin, hydrous wool fat (lanolin) and sulfonated olive oil. From this group different combinations were compounded. The following ointments were selected, since they were not too greasy or too stiff:

Formula 1

	Per Cent
Petrolatum	70.0
Hydrogenated cottonseed oil	30.0

Formula 2

(A modification of simple ointment U. S. P.)

White wax [16]	5.0
Glyceryl monosterate [14a]	12.5
Hydrous wool fat	5.0
Sodium silicate, commercial solution	5.0
Ammonium hydroxide, 10% solution	0.5
Petrolatum	72.5

The ammonium hydroxide is incorporated to prevent precipitation of the sodium silicate.

Formula 3

The preceding preparation is enhanced by the addition of 5 per cent (by weight) of latex, which produces a rubbery film on the skin. The base is melted, latex is added during stirring, and the stirring is continued until congelation occurs.

Formula 4

The following preparation has a p_H of 5.4 and is therefore recommended when there is prolonged contact of the hands with soapy water.

	Per Cent
White wax	10.0
Hydrous wool fat	5.0
Glyceryl monostearate [14a]	12.5
Stearic acid	2.0
Petrolatum	75.5

14. This phase of the work was done by Aaron Lichtnin, Ph.G., who made valuable suggestions.

14a. Glyceryl monostearate may be obtained as Xerol A (Fries Brothers).

15. Latex is the milk juice of the trees that are used to supply rubber. We employed the preparation lotol Nc 957, Naugatuck Chemical Company, New York, which consists of 60 to 63 per cent concentrated latex.

16. The white wax employed in this and all other formulas was white wax U. S. P.

Formula 5

The following preparation to water-proof the skin is recommended when there is prolonged contact with water.

	Per Cent
White wax	10.0
Hydrous wool fat	5.0
Sulfonated olive oil [17]	10.0
Petrolatum	75.0

Group 2.—Formulas 6, 7 and 8 are clean nongreasy preparations that dry on the skin and do not rub off. Their use is indicated, therefore, in dry work, as a protection against dust-borne irritants or when soiling of material or objects by the protective is not desirable. Formula 6 is smeared on the skin, whereas formulas 7 and 8 are liquids and are applied by means of a brush or swab.

Formula 6	Per Cent
Glyceryl monostearate [14a]	12.0
White wax	12.0
Wool fat	6.0
Cholesterol	1.0
Sodium silicate, commercial solution	5.0
Ammonium hydroxide, 10% solution	0.5
Water	63.5

Melt white wax, glyceryl monostearate, hydrous wool fat and cholesterol in one pot. Add sodium silicate solution and ammonium hydroxide solution to water previously heated in another pot. Stir aqueous solution into the wax mixture.

Preparations of mastic solution in acetone dry and leave a film on the skin.

Formula 7	Per Cent
Ethyl cellulose	5.0
Mastic	8.0
Castor oil	1.0
Acetone (technical) [18]	86.0

Formula 8	Per Cent
Polyvinyl acetal resin (Monsanto Chemical Co.)	5 to 10.0
Castor oil	1.0
Acetone (technical) [18]	89 to 94.0

In both these formulas use whole mastic, not the powder. Allow the mastic to stand in acetone overnight. A residue remains. Use supernatant fluid as a solvent for the other ingredients.

In formula 7 ethyl cellulose [19] was regarded as more desirable than pyroxylin or myrrh, the use of which was studied. In formula 8 an alkyd resin (rezyl 19, American Cyanamid and Chemical Co.) was not superior to the vinyl resin employed. Neither formula is entirely

17. The type known commercially as 75 per cent.

18. The more expensive, chemically pure grade could also be used.

19. Dr. James H. Sterner, of the medical department of the Eastman Kodak Company, stated that from extensive experience with workmen exposed to ethyl cellulose, this chemical has a low sensitizing capability.

removed by washing, but the residue is readily removed by acetone. If the latter is employed, an emollient should be used, especially in winter.

Group 3.—Another type of protective is a thick paste that leaves a water-proof, impervious covering.

Formula 9	Per Cent
Zinc oxide	25.0
Kaolin	25.0
White petrolatum	50.0

This preparation affords more protection than any of the other formulas, and it also water-proofs the skin. Its disadvantages are that it is somewhat sticky and it soils objects in contact with it, since it rubs off to some degree. It is therefore appropriate only in certain work.

OTHER PROTECTIVE APPLICATIONS

Hydrous wool fat (lanolin) has been effective in preventing cancer in experiments in which carcinogenic agents were applied. This fact is in keeping with the observation that animal and vegetable oils do not act as carcinogenic agents and that the natural cutaneous fat is an important factor in the prevention of experimental cancer.

It was shown by the Tworts [20] in experimental studies that equal parts of olive oil and wool fat (anhydrous) made the most efficacious ointment for protection from the carcinogenic action of mineral oils and tars. It was recommended that this mixture be applied to the exposed skin of workers handling carcinogenic oils, tars and most of their products before commencing work, and that at the end of the work day the soiled skin be thoroughly washed with soap and water and that hydrous wool fat again be applied.

In addition to personal cleanliness and frequent washing of the exposed parts, different applications have been recommended for the prevention of dermatoses in those who work with petroleum and lubricating oils. Scott [21] recommended crude castor oil, since it is impervious to paraffin. Downing [2] advised the application of greaseless creams and of equal parts of boric acid solution and alcohol before and after work. Dusting the arms with equal parts of starch and powdered zinc oxide has been suggested.[22] In Bridge's [23] experience, washing

20. Twort, C. C., and Twort, J. M.: The Utility of Lanolin as a Protective Measure Against Mineral Oil and Tar Dermatitis and Cancer, J. Hyg. **35**:130, 1935; On Prevention of Mineral Oil and Tar Dermatitis and Cancer, Lancet **1**:286, 1934.

21. Scott, A.: The Occupational Dermatoses of the Paraffin Workers in Scottish Shale Oils, Brit. M. J. **2**:381, 1922.

22. Memorandum on Cutting Lubricants and on Skin Diseases Produced by Lubricants, Bulletin 2, Department of Scientific and Industrial Research, London,

(Footnotes continued on next page)

with dilute solution of sodium hypochlorite before and after work was an effective preventive measure, which was doubtless directed against some infectious agent in the oil, although this cause of oil dermatosis is questionable. McConnell [24] advocated the application of hydrous wool fat or equal parts of hydrous wool fat and castor oil. In Hausser's [25] experience the best results were obtained with the application of glycerin before work and after work a solution containing sodium bicarbonate 20 Gm., glycerin 5 cc., chlorine 3 Gm. and water 100 cc.

Shepard and Krall [26] advised the application of an alkaline solution, such as sodium bicarbonate, to the arms of persons working with rubber in order to neutralize the acid of the sweat and thus to prevent dermatitis from methenamine (hexamethylene tetramine). This accelerator, however, is being replaced by less dangerous ones.

Horner [3] recommended that cottonseed oil be applied to the hands before exposure to paint and printing ink in order to facilitate their removal from the skin. For a similar purpose McConnell [27] advised that equal parts of hydrous wool fat and olive oil be applied to the hands and arms of printers before they commence work. He concluded from his studies that the mechanical removal of ink by brush is responsible for the initiation of dermatitis among printers, and not adulterants of oil of turpentine.

We advise workmen whose hands become soiled to apply before commencing work olive oil, neat's foot oil, hydrous wool fat or linseed oil. Such application facilitates the removal of dirt, grease and grime, especially if one of these oils is applied again to the soiled parts and removed with a clean cloth before washing with soap and water.

In prevention of dermatitis from wood-preserving materials in which coal tar distillate, water gas tar and zinc chloride are the substances regarded as the causative agents, the application of hydrous wool fat containing 10 per cent sodium bicarbonate has been recommended.[28]

1918, p. 8; cited by Downing, J. G., and Welch, C. E.: New England J. Med. **206**: 666 (March 31) 1932.

23. Bridge, J. C.: Occupational Diseases of the Skin, Brit. M. J. **2**:324, 1933.

24. McConnell, W. J.: Dermatoses Following the Use of Cutting Oils and Lubricating Compounds, Pub. Health Rep. **37**:1773, 1922.

25. Hausser, G.: Les dermatoses professionelles dues aux huiles de graissage, Presse méd. **46**:295, 1938.

26. Shepard, N. A., and Krall, S.: Poisons in the Rubber Industry: The Rash Produced by Hexamethylene-Tetramine and a Means of Prevention, J. Indust. Hyg. **2**:33, 1920.

27. McConnell, W. J.: Industrial Dermatitis Among Printers, Pub. Health Rep. **36**:979, 1921.

28. Dermatitis from Wood Preserving Materials, Queries and Minor Notes, J. A. M. A. **97**:799 (Sept. 12) 1931.

The application to the hands of pine tar as a protection (?) against lime is a traditional remedy (without scientific basis) used by workers in tanneries (case 11).

A solution of sodium bisulfite ($NaHSO_3$) as a reducing agent is an effective remedy. Its use is especially indicated before and after exposure to chromic acid and chrome compounds, since it reduces them to the non-irritating chromous state. In this regard, White [29] advised that a concentrated solution be allowed to dry on the skin before exposure and that a strong solution be used as a wash after exposure. He recommended as a general rule that in all industries involving exposure to chemicals, dyes, drugs, coloring materials, irritating dusts or fluids the hands be swilled in a solution of sodium bisulfite preparatory to the ordinary washing and also after using the commonly employed mixture of anhydrous sodium carbonate (soda ash) and calcium hypochlorite (hypochlorite of lime) to remove stains caused by dyes.

HARMFUL AND HARMLESS METHODS OF CLEANSING THE SKIN

Neutralizing Solutions and Applications to be Used After Work.—A common practice among industrial workers is to use on the hands, for removing dye, paint or other stains, solvents or chemicals that are used in their work (cases 4, 5 and 8). Such cleansing agents are either primary cutaneous irritants or sensitizing or defatting substances, and those usually employed are turpentine, alcohol, wood alcohol, naphtha, acetone, amyl acetate, gasoline, kerosene, benzine, calcium hypochlorite and various acids and alkalis. Workers whose occupations require the use of paint, varnish, stain or lacquers invariably use turpentine, paint thinners or a solution of sodium carbonate. Machinists use kerosene; automobile mechanics, gasoline. Printers, type setters and lithographers employ type wash, turpentine or kerosene. The practice in dye houses or where coloring material is handled is to remove the dye or stain with a bleaching solution: calcium hypochlorite or sodium hypochlorite. The following are commonly employed trade formulas: one pound (0.45 Kg.) each of anhydrous sodium carbonate (soda ash) and calcium hypochlorite to 3 gallons (11.36 liters) of water (this amount or less of sodium carbonate alone suffices), and for acid dyes, 63 Gm. of sodium hypochlorite, 5 Gm. of sodium chloride and 15 Gm. of sodium hydroxide to 1 liter of water. If these methods are employed, solutions of minimum strength should be used, followed by rinsing in running water and immersion of the hands or forearms in a solution of sodium bisulfite ($NaHSO_3$).

29. White, R. P.: The Dermatergoses, or Occupational Affections of the Skin, ed. 4, London, H. K. Lewis & Co., Ltd., 1934, p. 339.

A harmless yet efficacious method of removing dye or other stain is the free application of a 10 to 30 per cent solution of sodium bisulfite ($NaHSO_3$). If this does not suffice, it should be used after the application of a 1:2,000 to 1:4,000 solution of potassium permanganate. If sodium bisulfite solution is allowed to dry on the skin before beginning work stains are more easily removed.

To remove such substances as paint, oils and grease, a 1 to 2 per cent solution of a commercial solution of sodium silicate or, what is superior to this, a 0.5 to 1 per cent solution of sodium metasilicate can be employed. The latter chemical should be considered in the removal of any foreign substance from the skin and as a general cleanser.

During or after exposure of the hands to acids or alkalis the following noninjurious solutions should be employed: for acids, a saturated solution of either sodium bicarbonate or sodium borate ($Na_2B_4O_7$), and for alkalis, a 3 to 4 per cent solution of acetic acid or a saturated solution of boric acid. A good method of removing from the skin stains caused by trinitrophenol (picric acid) is the application of a paste of magnesium carbonate.[30]

In the prevention of "photographer's dermatitis" the British Chief Medical Inspector of Factories in his report for 1929 advised that after exposure to metol (a proprietary photographic developer, methylaminocresol sulfate) the hands should be immersed in a weak solution of a mineral acid and that in subsequent washing no soap containing a free alkali should be employed. In an attempt to prevent dermatitis from contact with developing solutions at the Eastman Kodak Company, the Medical Director[31] of the Eastman Park Works informed us that rinsing in a 1 to 3 per cent solution of acetic acid is practiced after exposure, followed by rinsing with a great deal of water.

The application of bland oils (olive, cottonseed and linseed oil and liquid petrolatum) has long been advised in order to facilitate the removal of dirt prior to the use of soap and water.[32] The addition of one of these oils or of liquid soap to sawdust has been advised. Sulfonated oils, either olive or neat's foot, mixed with an equal part of liquid petrolatum are preferable to the aforementioned ones.

The use of an abrasive soap or of a hand brush is mechanically irritating and should therefore be avoided.

We advise the following formula as a substitute for the popular mechanic abrasive soaps. Equal parts of sulfonated neat's foot oil and liquid petrolatum containing 25 per cent gelatin (formula 12) are

30. Dermatitis from Trinitrophenol, Queries and Minor Notes, J. A. M. A. **95**: 1284 (Oct. 25) 1930.

31. Slater, B. J.: Personal communication to the authors.

32. Emulsified preparations dispensed as cosmetics have been exploited as cleansing agents. These, however, have no place as cleansing agents in industry.

added to white granulated corn meal [33] in the proportion of 1½ parts, by weight, of corn meal and 1 part, by weight, of the oil mixture. To prevent growth of mold or bacteria a 0.5 per cent solution of chlorobutanol is added. Corn meal of a wide variety of particle sizes is obtainable. White granulated meal was selected, since the particle size was adapted for abrasive purposes. The corn meal and oil mixture has the appearance of wet sand. The p_H of the mixture is about 5. As a detergent it is used with water in the same manner as is soap. The addition of 1 to 2 per cent sodium hexametaphosphate (p_H 6) or 2 per cent sodium metasilicate enhances the preparation when employed to cleanse particularly dirty or greasy hands. With the addition of 2 per cent sodium metasilicate the p_H of the mixture was 7.1. It is not desirable to make the mixture alkaline by the addition of mineral detergents. We doubt the necessity of this, since in our observation the mixture alone cleaned soiled hands of workmen as effectively as does any abrasive soap. After its use soap is not necessary. The mixture acts not only as a detergent but as an emollient.

Another substitute, although less desirable since it is alkaline, is the following: To cleanse soiled, especially oily and greasy, hands, they are first immersed in a 1 per cent solution or less of sodium metasilicate and then washed with a mixture of equal parts, by weight, of flaked (chip) soap and granulated corn meal.

It is advisable that sulfur soap rather than any other soap be used by workmen exposed to lead.

In our survey less than 10 per cent of the workmen apply an emollient to the hands in winter at the end of the work day. For this purpose we advise equal parts of hydrous wool fat and olive oil, cottonseed oil or neat's foot oil.

SOAP AS A DETERGENT

The custom among workmen is to use the same soap for washing their hands that is used for industrial or for purposes other than toilet in their place of employment (cases 1, 2, 6 and 7). Usually such soaps are not appropriate for toilet purposes.

Mechanic Soap.—In our observations the most frequently employed soap by workmen whose hands become soiled is a well known abrasive (grit) cake soap (p_H 8.2) or a well known abrasive soap paste (p_H 10).

We were able to find, and gave consideration to, forty-four commercially available mechanic soaps. Of these forty-four, seventeen are abrasive pastes (hand grit paste soap), fifteen are gritty powders (hand scouring powder), four are abrasive (grit) cake soaps, three are liquid,

33. The manufacturer informed us that no bleaching agent or other ingredient is contained in corn meal. In preparing the corn for the production of corn meal, only the germ and part of the bran are removed.

two are ointment-like and one is a soft soap. The abrasive agent in these soaps is probably inorganic: pumice, silicon dioxide (silica; silex) or sand. There is at least one exception, in which the abrasive agent is corn meal. The hydrogen ion concentrations of 1 per cent aqueous solutions of these soaps range from 8.2 to 10, with one exception, in which the p_H is 3 and which is therefore not soap in the sense of a saponified vegetable or animal oil.

Federal specifications [34] for a hand grit soap allow free alkali 0.1 per cent, alkaline salts (calculated as sodium carbonate) not to exceed 1 per cent and insoluble siliceous material not less than 25 per cent or more than 40 per cent; for a hand grit paste soap and hand scouring powder, sodium carbonate not to exceed 2 per cent, free alkali 0.02 per cent, anhydrous soap not less than 8 per cent or more than 16 per cent and insoluble siliceous material not less than 25 per cent or more than 50 per cent.

Mechanic soaps usually contain sodium silicate in large quantities, as much as 25 per cent; others contain sodium sesquicarbonate, sodium tetraborate, trisodium phosphate or sodium carbonate.

Most writers advise against the use of abrasive (grit) soaps. Until another equally effective and quick method is offered and workmen are educated in regard to it, abrasive (grit) soaps will continue to be popular. We believe that the aforementioned sulfonated oil and corn meal mixture is a good substitute for abrasive soaps.

In such instances in our observations in which the employer provided soap for the employees it was not apparent to us that any discrimination was used in selecting the soap. Most frequently a liquid soap was provided.[35] Liquid soaps are usually high in coconut oil content. This is an undesirable feature. Lay persons are not in a position to know what constitutes a good soap, and unbiased information is not easily obtained.[36]

Toilet Soap.—In prevention of industrial dermatitis some writers recommend "a neutral soap," "a soap not too strongly alkaline" or "a good toilet soap." What is a good toilet soap? Federal specifications

34. Federal specifications for soaps quoted in this paper are those of the United States Bureau of Standards, Department of Commerce, and were supplied (from catalog) by the Superintendent of Documents, Government Printing Office, Washington, D. C. The specifications apply only to soap sold to the Goverment and not to any soap commercially available.

35. The fact that liquid soap, in contrast to cake soap, cannot be taken away from the place of employment is an important consideration.

36. One exception is the information presented by Consumer's Research, a bureau organized on a noncommercial basis to provide unbiased information and counsel on goods bought by the ultimate consumer. Particular reference is made to the following volume: Phillips, M. C.: Skin Deep, New York, The Vanguard Press, 1934.

for a good, commercially made soap for toilet use are that it should be as free as possible from water, lather freely with cold soft water, be free from rosin, sugar and other foreign matter and contain not more than 0.1 per cent free alkali. The specifications allow as much as 15 per cent of the net weight to be water.[37]

Coconut oil, the chief oil or fat ingredient in most toilet soaps,[38] is generally regarded as irritating to most skins. This prompts some manufacturers to keep the percentage of cocoanut oil lower than 20 per cent of the oil used in the manufacture of toilet soap. Consumers Research has advised that coconut oil should comprise not more than 20 per cent of the oil in toilet soap. Weber [39] advised the use of not more than 10 per cent of coconut oil. The formulas he published of the perfect toilet soap comprised, in addition to coconut oil, slightly hardened oil,[40] palm oil, castor oil and olive oil.

Blank [41] suggested that the saturated fatty acids of lower molecular weight (caproic, capric and caprylic) contained in coconut oil constitute its irritating agent, since these fatty acids are primary cutaneous irritants, and also that fatty acids in soap, in relation to the hydrogen ion concentration, are responsible for the irritating action of soap. He performed patch tests with fatty acids in conjunction with a buffer solution to duplicate the increase in the p_H of the skin (6 to 7.5) which occurs after washing with soap. He observed that on skin of a p_H higher than that of normal skin the fatty acids of higher molecular weight produced irritation, whereas they did not irritate the normal skin. Not only does the irritating quality of the fatty acids decrease with an increase in the molecular weight, but also the amount of alkali which must be added before a fatty acid becomes an irritant increases with the increase in the molecular weight of the fatty acid. He stated that a soap to be nonirritating should contain no fatty acid which will be irritating to the "alkalinized" skin and certainly no fatty acid which is itself an irritant to skin with a normal p_H. Such soap should be made only from palmitic and stearic acids.

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37. The relative economy of soaps is measured by the cost per pound of dry soap.

38. An exception is soap in which pure olive oil is the sole oily or fatty ingredient. The term castile formerly implied this. It no longer does, since judicial verdict permits the use of the word castile without this specification.

39. Weber, K. L.: Die volkommene toiletten Seife, Ole, Fette Wächse Seife, Kosmetik **5**:1, 1937.

40. The nature of the hardened oil is not stated. It doubtless refers to the hydrogenation of liquid oils which stiffens (hardens) them. Such hardened oil is usually added to the natural oil.

41. Blank, I. H.: Action of Soap on Skin, Arch. Dermat. & Syph. **39**:811 (May) 1939.

Neutral Soap.—A "neutral soap" is one in the manufacture of which the amounts of alkali and of fatty acids are in exact molecular proportion, so that the finished product contains no free alkali or free fatty acid. The word "neutral" does not refer to the compound soap, which is not neutral in the chemical sense. Since soap is the salt of a weak acid (fatty) and a strong alkali (sodium or potassium hydroxide), it is, in accordance with chemical laws, alkaline. It is difficult to manufacture a "neutral" soap. Indeed, such soap is more of theoretic than of practical importance.

Concerning a "neutral soap," Bleyberg and Lettner [42] concluded that the differences in actual alkalinity of solutions of different soaps at the same temperature, as well as of the same soaps at different temperatures (20 to 90 C.) or concentrations, were many times greater than the differences in alkalinity through the presence in the soap of a few tenths per cent of free alkali. Thus the stringent technical requirements of a minimum amount of free alkali in soaps appears unfounded. It would be better to fix the $p(OH)$ concentration instead.

All soaps, whether neutral, superfatted [43] or containing a minimum amount of free alkali, hydrolyze in aqueous solution and are always alkaline. The alkali of hydrolysis is much greater than the amount of free alkali in the soap. Too much emphasis, therefore, need not be placed on neutral soaps or on a minimum amount of alkali as an index of good soap. We determined the p_H of a 1 per cent aqueous solution (with distilled water) of thirty-six toilet soaps. The range was from 9 to 11.

A number of investigators have shown that the hydrogen ion concentration of the skin is increased after the use of soap. This is attributed to absorption of alkali by keratin. The return of an acid cutaneous reaction usually occurs after several hours. It is this interference with the protective "acid mantle" of the skin that constitutes, with the defatting action, the chief objection to soap.

The "alkalization" of the skin after the use of soap suggests the use of a weak acid solution, such as 1 to 3 per cent acetic acid, as a

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42. Bleyberg, W., and Lettner, H.: Die Alkalität verdünnter wässeriger Seifenlösungen und ihre Beeinflussung durch Zusätze freien Alkalis, Chem. Umschau. d. Geb. d. Fette, Oele, Wächse Harze **39**:241, 1932.

43. "In order to guard against the presence of free caustic soda [sodium hydroxide] in the finished soap, some makers add olive oil or (and) wool wax [wool fat], on the assumption that the caustic soda will combine with them to form neutral soap. These soaps are known as "superfatted soaps" (Lewkowitsch, J. I.: Chemical Technology and Analysis of Oils, Fats and Waxes, ed. 6, revised by G. H. Warburton, London, Macmillan & Co., 1923). Superfatting agents have little influence after hydrolysis of soap. We believe that superfatted soap has been unduly emphasized as a toilet soap.

buffer application, especially after prolonged contact with soap and water. In this regard, Jones, Murray and Ivy [44] suggested the use of a 1 per cent solution of sodium hexametaphosphate,[45] a salt of one of the polymers of metaphosphoric acid which has the property of forming a soluble nonionized complex with the alkaline earths. In solution this salt has a p_H of 6 and can buffer the skin at this acidity against a large amount of alkali.

Mangrané [46] and also Lustig and Schmerda [47] stated the belief that the degree of hydrolysis of soap is important in relation to its mildness. The degree of hydrolysis depends on the type of fatty acid and also on the alkali. Soaps with slight hydrolysis, such as those made with coconut oil and castor oil and not easily soluble in water, exert a greater defatting action, since the skin comes in contact with larger amounts of soap. Mangrané [46] advised that pure cocoanut oil soaps should be used only by persons with an oily skin. Potassium soaps usually hydrolyze more than sodium soaps. This would therefore suggest that shaving soaps are less irritating than toilet soaps. Indeed, it is the consensus that shaving soaps exert a milder action on the skin than toilet soaps.

Lustig and Schmerda [47] determined the hydrogen ion concentration and fatty acid and sodium contents of various soap solutions in order to ascertain the degree of hydrolysis. It was observed that sodium stearate and sodium palmate hydrolyze strongly and that their solutions are strongly alkaline to phenolphthalein. With increasing concentration of the soap, hydrolysis became less. It was lower also when the molecular weight of the saturated acids was low or when the acids were unsaturated. Hydrolysis was also less if the fatty acids present were of several kinds. The addition of an unsaturated acid to stearic acid diminished the solubility of the unsaturated fatty acid and increased that of the saturated fatty acid.

Kröper [48] stated the belief that an osmotic phenomenon between soap fluid and the skin is a factor in the irritating action of soap. He studied the dialysis of potassium soaps with different fatty acids,

44. Jones, K. K.; Murray, D. E., and Ivy, A. C.: Sodium Hexametaphosphate: Its Use for Certain Industrial Dermatoses, Indust. Med. **6**:459, 1937.

45. Sodium metaphosphate products are marketed by Calgan, Inc., Pittsburgh.

46. Mangrané, D.: Substitución del radical potásico por el sódio y vice-versa en los jabones alcalinos, Soc. españ. de fis. y quim. **32**:893, 1934; cited by Pfaff, K.: Aus dem Notizbuch des Seifentechnikers, Riechstoffindustrie u. Kosmetik **10**:200, 1935.

47. Lustig, B., and Schmerda, F.: Ueber die Löslichkeit der Natriumseifen: Ein Beitrag zur Pharmakologie der Seifenwirkung, Dermat. Wchnschr. **104**:607, 1937.

48. Kröper, H.: Ueber das Verhalten der Lösungen von Seifen und Netzmitteln an halbdurchlässigen Membranen, Dermat. Wchnschr. **106**:381, 1938.

employing a semipermeable membrane. It was observed that hydrolysis and dialysis were in inverse ratio—the more limited the hydrolysis, the greater the dialysis. One of his specifications of a good detergent is that it should have a low dialysis index.

Lewkowitsch [49] stated that the best class of toilet soaps contain as a rule 80 per cent fatty acids. The range in cheap toilet soaps is down to less than 40 per cent. For household purposes all qualities are made, from genuine soap containing 63 per cent fatty acids down through all gradations of carbonated, silicated, "filled" and "run" soaps to "scouring" soaps, which may contain only 10 per cent of fatty acids.

The following soaps are at times employed by workmen. Of these, soap powder is the most harmful.

Scouring Soaps.—These are prepared from coconut oil, to which may be added kitchen grease, saponified with sodium hydroxide (caustic soda). Sodium silicate and anhydrous sodium carbonate (soda ash) are additional ingredients, and colloidal clay or fullers' earth are sometimes added. For abrasive purposes silicon dioxide (silica; silex) powder is incorporated. Federal specifications for a grit cake (scouring) soap allow 0.1 per cent free alkali (calculated as hydroxide) and 1 per cent alkaline salts (total alkalinity of matter insoluble in alcohol) calculated as sodium carbonate, with the insoluble siliceous material not less than 88 per cent or more than 93 per cent.

Soap Powder and Washing Powder.[50]—Soap powder is a mixture of hard soap and sodium carbonate and frequently contains sodium silicate, sodium borate (borax), trisodium phosphate or other builders. Some contain a bleaching agent. The soap in some is made of cottonseed oil. Soap powders usually contain 15 to 20 per cent soap, as much as 55 per cent sodium carbonate and 10 per cent water. Federal specifications require not less than 15 per cent soap and not less than 30 per cent sodium carbonate. Some of the more recent soap powders contain more soap, as much as 60 per cent, and 30 per cent or less of mineral detergents.

Laundry or Household Soaps.—Depending on the grade, these soaps are made of mixed fatty oils (coconut, palm kernel, tallow, cottonseed oil), hydrogenated oils or fatty material of low quality, such as kitchen or packing house grease and bone fat, which are fatty acids of low molecular weight. Sodium carbonate or sodium borate (borax) and

49. Lewkowitsch, J. I.: Chemical Technology and Analysis of Oils, Fats, and Waxes, ed. 6, revised by G. H. Warburton, London, Macmillan & Co., 1923, vol. 3, p. 352.

50. Soap powder should be distinguished from "powdered soap," which includes soap chips, soap flakes, granular soaps and soap beads also employed for household uses.

sodium silicate up to about 15 per cent are used in yellow bar soaps. Federal specifications for the ordinary grade allow up to 0.5 per cent free alkali, with not less than 2 per cent or more than 10 per cent alkaline salts.

Soap Chips or Flakes.—This class contains more soap (80 per cent or more) and less alkaline salts than any of the aforementioned soaps. Federal specifications allow 15 per cent water and 3 per cent alkaline salts.

Ingredients of Soap.—"Fillers."—"In soap making by the word 'filling' is understood the art of producing cheaper soaps by the mechanical addition of cheaper substances." [51] The number of substances which are now incorporated in soaps so as to impart to them either some actual or assumed valuable property is legion.

In the opinion of Lewkowitsch [52] soaps containing less than 50 per cent of fatty acids should be looked on as "adulterated," whether the fillings have detergent properties or not, unless the admixture be declared openly.

It is difficult to define what really constitutes an adulteration of soap. This has been a matter of controversy in trade and in judicial circles, particularly regarding sodium silicate. To serve a purpose regarded desirable by some manufacturers a variety of fillers may be added. For example, alcohol, castor oil, or glycerin and sugar are used for making transparent soaps.

Filling Materials.—These consist essentially of salts soluble in water, such as sodium and/or potassium chloride and sodium and/or potassium sulfate; alkali carbonates; silicates; mineral substances, such as talc, titanium and/or zinc oxide; sodium and/or barium sulfate; silicious materials, and organic substances, such as potato starch.

Silicates of Sodium.[53]—Sodium silicate is an important ingredient of soap. In addition to its presence in household and mechanic soaps, as already discussed, some toilet soaps contain 1 to 4 per cent. Soaps made from certain fat stocks become rancid on exposure to air. The presence of silicate prevents this. In addition it is added to soap to whiten and harden it, to produce a firm, smooth texture and to increase the lather, emulsifying power and detergency. It is therefore maintained that silicate is a "builder" and not a "filler."

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51. Deite, C.: Manual of Toilet Soapmaking, ed. 2, translated by A. H. J. Keane, London, Scott, Greenwood & Son, 1920, p. 143.

52. Lewkowitsch,[49] p. 344.

53. Richardson, A. S.: The Action of Sodium Silicate When Used in Soap, Indust. & Engin. Chem. **15**:241, 1923. Stericker, W.: The Value of Silicate of Soda as a Detergent, ibid. **15**:244, 1923. Vail, J. G.: The How and Why of Silicate of Soda, Soap **4**:18, 1928; Soluble Silicates in Industry, American Chemical Society Monograph, New York, Reinhold Publishing Company, 1928.

In the manufacture of soap, the 40 per cent commercial solution of sodium silicate is employed. It is not a definite chemical compound but a combination of different relative amounts of sodium monoxide and silicon dioxide (silica). We noted by patch tests that the commercial solution is not a primary cutaneous irritant.

Sodium metasilicate [54] (more properly sodium metasilicate pentahydrate, $Na_2SiO_3.5H_2O$) and sodium sesquisilicate [55] ($3Na_2O.2SiO_2.11H_2O$, or the pentahydrate of trisodium orthosilicate) are definite chemical compounds that have a power for wetting surfaces and emulsifying oils and are deflocculating agents. They are therefore detergents and are used for a variety of industrial purposes (in laundries and in washing bottles, dishes, metals, machinery and garage floors) alone or with soap.

A 1 to 2 per cent solution of a commercial solution of sodium silicate or a 1 per cent solution or less of sodium metasilicate placed in the palms and rinsed with water serves as a detergent.

We performed patch tests on normal persons with 2, 4 and 6 per cent solutions of sodium metasilicate. Negative results were obtained.[56] A 25 per cent solution produced a mild erythema only on some persons.

ALLERGENIC ACTION.—We do not believe that the compound soap is allergenic. Excluding medicated soap, the notable allergenic ingredients of soap are dyes, perfumes, essential oils and possibly the salts of rosin acids.[57]

Cutaneous Irritants.—The factor causing soap to be a primary cutaneous irritant may be the fatty acid, as suggested by the work of Blank.[41] On the other hand, Lewkowitsch and Warburton [58] stated that the quantities of free fatty acid that are liberated after hydrolysis of soap

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54. Sold under the trade name of metso (Philadelphia Quartz Co., Philadelphia).

55. Metso 99.

56. Although sensitization to silicates of sodium has been reported (Blaisdell, J. H.: Medicolegal Complications in Dermatology Caused by Massachusetts Workmen's Compensation Act, Arch. Dermat. & Syph. **39**:77 [Jan.] 1939), it is apparently rare.

57. Rosin is the resinous matter remaining after distillation of the volatile oil from turpentine. It is used as a cheap substitute for fatty matter in the manufacture of soap, since the alkali salts of rosin acids have detergent properties. Rosin imparts a yellow color to soap and is used in the manufacture of yellow laundry soap bars.

58. "When dissolved in water soap suffers hydrolysis to an extent dependent on the dilution, resulting in the precipitation of acid soaps (e. g. sodium hydrogen palmitate) and the liberation of a small amount of free alkali and infinitesimal quantities of free fatty acid." (Lewkowitsch, E., and Warburton, G. H.: Soap, in Encyclopaedia Britannica, ed. 14, New York, Encyclopaedia Britannica, Inc., 1937, vol. 20, p. 858).

are infinitesimal. In spite of the statements in the literature to the contrary, we do not believe that the alkalinity per se acts as a cutaneous irritant.

Cake soap (laundry, household or mechanic) is not sufficiently soluble to allow the alkaline salts contained in it (fillers and builders) or indeed any other ingredient in sufficient concentration in the soap solution to act as a primary cutaneous irritant. Soap used for washing hands is employed in solution of 1 per cent or less and in not much greater percentage for household purposes.

The foregoing statement applies to all soap in which the alkaline salts are added after the fats and alkali have been combined. Alkaline salts mixed with the finished soap to constitute soap powder or mixed with abrasive material to constitute gritty powders (hand scouring powder) for mechanic use may be more likely to act as cutaneous irritants by reason of their ready solubility.

To our knowledge, the concentration, if any, of all the alkaline salt detergents used as fillers or builders that acts as a cutaneous irritant has not been determined. We observed by patch tests that the normal skin did not react to a 35 per cent solution (saturated at room temperature) of anhydrous sodium carbonate. The results of patch tests with the other alkaline salt detergents thus far suggest that even in saturated solution they are not primary cutaneous irritants. The role of alkaline salt detergents as cutaneous irritants, we believe, is not inherent to their employed strength but concerns prolonged exposure of the skin to them, whereby they become irritants either because the threshold of irritability of the skin is lowered (toxic hypersensitivity in the sense of Burckhardt) or because the skin becomes allergic to them.

In Burckhardt's [59] studies of the sensitivity of the skin to alkali, its capability to neutralize alkali and the eczema due to alkali, notably that of masons, he concluded that decreased resistance of the skin to alkali (toxic hypersensitivity) is an important etiologic factor in this form of eczema rather than an allergic hypersensitivity. Toxic hypersensitivity concerned impaired function of the skin to neutralize alkali.

Burckhardt's studies suggest that dermatitis from soap in its broadest meaning and from alkaline cleansers other than soap, as herein discussed, concerns a toxic hypersensitivity rather than an allergic hypersensitivity. His studies emphasize the fact that alkaline detergents are not ideal. They should be used sparingly or in minimum concentration. The importance of applying buffer applications to the skin after their use, as previously discussed, becomes apparent.

59. Burckhardt, W.: Beiträge zur Ekzemfrage: Die Rolle des Alkali in den Pathogenese des Ekzems speciell des Gewerbeekzems, Arch. f. Dermat. u. Syph. **173**:155, 1935; Das Maurerekzem (Eine experimentelle und klinische Studie zur Ekzemfrage), ibid. **178**:1, 1938.

SUMMARY.—It would appear that the best soap for cleansing the skin is a toilet cake soap. Basic factors constituting the eczematogenous action of soap are its defatting action inherent to excessive use and/or prolonged exposure, and prolonged exposure to alkaline salts not incorporated in soap but loosely combined as in soap powder. It is not unreasonable that the chief difference in the irritating action of toilet soap and laundry soap (in cake or bar form) is the fact that exposure to laundry soap is much more prolonged. Excluding all soap in powder form that contains alkaline salts, the role of soap used for toilet purposes as an eczematogenous substance has doubtless been exaggerated, in view of its universal and frequent use, the dilute solution of soap and its ingredients.

DETERGENTS OTHER THAN SOAP

Triethanolamine Soap.—Triethanolamine forms a salt with fatty acids and may be employed to make nonalkaline base soap.[60] Such soap has been suggested as a detergent to replace ordinary soap. Fiero [61] studied the detergency of pure salts of triethanolamine. The following had detergent action, not as great, however, as that of ordinary soap: laurate, oleate, myristate, palmitate and salts of commercial mixed fatty acids (of tallow, coconut oil and red oil). Triethanolamine salts have an alkaline reaction in aqueous solution, and therefore their use as a detergent does not overcome this objection to ordinary soap. Exceptions, however, are the salts of isocaproic, caproic, caprylic and capric acids, the p_H of which Fiero observed ranged from 6.1 to 6.4.

Acid Soap.—So-called "acid" soap [62] is made with naphthenic acids, which are recovered in the Russian oil industry from the "soda tar" obtained in the refining of petroleum fractions. Chief objections to this compound are the unpleasant smell of petroleum inherent to naphthenic acids, its low degree of hydrolysis and its poor detergent properties.

Laptev and Moldavskii [63] studied the action on the skin of "substitute" soaps prepared from naphthenic acids, resin acids, liquid synthetic acids, a mixture of fats with resin, and synthetic acids. It was noted that the detergent action of these preparations was less than that of ordinary soap; otherwise some of them compared favorably with ordinary soap, whereas others caused dryness of the skin or stickiness of the hair. Soaps made with naphthenic acids imparted a persistent unpleasant odor to the hair.

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60. Hetzer, J.: Alkalifrei Waschmittel, Öle, Fette, Wächse **9**:9, 1937.

61. Fiero, G. W.: Salts of Triethanolamine, J. Am. Pharm. A. **27**:658, 1938; Salts of Triethanolamine: II. Detergency, ibid. **28**:284, 1939.

62. Levinson, H., and Meunch, H.: Napthene Acid Soaps, Soap **14**:69, 1938.

63. Laptev, A., and Moldavskii, V.: The Action of Soaps on White (Cotton) Fabric and Human Skin, Masloborino zhir. delo **13**:30, 1937.

Sulfonated Oils.—More recently sulfonated oils have been employed as detergents for the human skin. Blank,[64] who has done pioneer work in this field, suggested this formula as a soap substitute: sulfonated mixed olive and tea-seed oil 25 per cent, light liquid petrolatum 25 per cent and water 50 per cent.[64a] The p_H of this mixture varies from 6 to 7.

We studied the detergent action of sulfonated olive oil, sulfonated castor oil and sulfonated neat's foot oil mixed with liquid petrolatum. We believe that sulfonated oils mixed with liquid petrolatum should be used with only a minimum amount of water. We selected three formulas:

Formula 10	Per Cent
Sulfonated olive oil[65]	55
Light liquid petrolatum	45
Gelatin, 25 per cent aqueous solution	10

The percentage of sulfonated olive oil required to obtain a clear mixture with liquid petrolatum varies with different lots. The range is 50 to 60 per cent of sulfonated olive oil and 40 to 50 per cent of liquid petrolatum. For this and for the following formulas, heat the oil mixtures on a water bath until clear; then add gelatin and stir until solution is effected.

Formula 11	Per Cent
Sulfonated olive oil (55 per cent) } (Formula 10)	
Light liquid petrolatum (45 per cent) } of this mixture	70
Sulfonated neat's foot oil[66]	20
Gelatin, 25 per cent aqueous solution	10

Formula 12	Per Cent
Sulfonated neat's foot oil	45
Light liquid petrolatum	45
Gelatin, 25 per cent aqueous solution	10

Formula 13	Per Cent
Formula 12	2 parts
Sodium lauryl sulfate, 20 per cent solution	1 part

The p_H range of these mixtures was: no. 10, 5.35; no. 11, 5.3; no. 12, 4.8, and no. 13, 4.9. Gelatin was added to all the mixtures as a homo-

64. Blank, I. H.: Action of Soap on Skin: III. Sulfonated Oils as Substitutes for Soap, Arch. Dermat. & Syph. **39**:821 (May) 1939.

64a. This preparation is commercially known as Nopco BDA (National Oil Products Co., Harrison, N. J.).

65. The sulfonated olive oil employed in this and the other formulas is known commercially as 75 per cent.

66. The sulfonated neat's foot oil employed in this formula and in the others was acidolene A (Martin Dennis, Newark, N. J.) and also the preparation of the Kali Manufacturing Co., 1410 North Front Street, Philadelphia. It is clear at room temperature, becomes turbid between 50 and 60 F. and solidifies between 45 and 50 F. Turbidity may be prevented by the addition of castor oil or of solvents which prevent the solidification of the fatty acids.

genizing agent. It enhanced the preparations from a pharmaceutic standpoint. We prefer formula 12, since it is a satisfactory detergent and exerts more of an emollient action. We use and recommend this formula. As already discussed, we selected it to add to corn meal as a substitute for abrasive mechanic soap. The odor inherent to neat's foot oil is considerably less in the sulfonated oil, so that this feature has not been an objection in our experience. Formula 13, containing sodium lauryl sulfate, lathers somewhat and is perhaps a better detergent, its disadvantage being that it exerts a slight drying action on the skin.

Sulfonated Esters, Ethers and Alcohols.—There is increasing scientific interest in organic compounds which have wetting, penetrating, emulsifying or detergent properties. These compounds, which may be classified broadly as sulfonated esters, sulfonated ethers and sulfonated alcohols,[67] have extensive use in industry. There are few data available as to their use as detergents for human skin. For this purpose we studied sodium lauryl sulfate and santomerse S (Monsanto Chemical Co.) and a 30 per cent aqueous solution of substituted aromatic sulfonic acids. The addition of one or the other of these compounds to the sulfonated oil mixtures we do not believe essentially improved them. Sulfonated organic compounds exert a defatting action on the skin and are in this respect comparable to soap.

The German preparation known as praecutan [68] is sold as a cutaneous detergent. It consists of sodium salts of fatty acid condensation products and sulfuric acid esters of high molecular fatty acids. It is a light brown liquid of oily consistency which foams with water. The p_H of the preparation we determined was 5. Bauer [68b] stated that only an insignificant number of his patients had an intolerance to the preparation.

Vegetable Meals.—The detergent property of oat meal flour is perhaps not sufficiently appreciated. Other somewhat similar detergents, with the action doubtless attributed to the fixed oils they contain, are almond meal (sweet almond) and powdered bitter almond,[69] pow-

67. Caryl, C. R., and Ericks, W. P.: Esters of Sodium Sulfosuccinic Acid, Indust. & Engin. Chem. **31**:44, 1939. von Antwarpen, F. J.: Detergent Properties of Ether Sulfonates, ibid. **31**:64, 1939. Tyler, C. A.: Sulfated Fatty Alcohols, Soap **10**:25 (March); 21 (April) 1934. Mullen, C. E.: The Newer Detergents, ibid. **13**:30, 1937.

68. (*a*) Theissen: Zur Verhütung von Olekzema, Anz. Maschinewes **59**:2, 1937. Hilgenfeldt: Beitrag zur Frage der Händereinigung, Zentralbl. f. Gewerbehyg. **15**:36, 1938. (*b*) Bauer, H.: Ueber Erfahrungen mit Praecutan als Wasch und Badezusats bei Hautkranken und Hautgesunden, Med. Klin. **2**: 1176, 1937.

69. Bitter almond is toxic if ingested.

dered soap tree bark (quillaja), powdered orris root [70] and to a lesser degree flaxseed meal. When these substances are used with water to cleanse the hands the result is relatively satisfactory. The detergent action of powdered orris root, we believe, is not generally known. Oat meal flour, especially when used with boric acid solution instead of water, is a good means of cleansing the hands of patients with eczema.

Mineral Detergents.—The detergent action of soap is mainly a colloidal phenomenon conditioned by its physical properties, especially its power of lowering the surface tension and emulsifying oils. Other substances having the same physical properties of soap exert detergent action. Some minerals belong in this category and are employed as detergents alone or incorporated in soap: colloidal clay, fullers' earth (mixtures chemically allied to clay), soapstone (French chalk, "Kheel"), sodium silicoaluminates (containing aluminum, silicon dioxide [silica] and alkaline earths), silicates of sodium, sodium carbonate, sodium bicarbonate, sodium sesquicarbonate, sodium borate (borax) and disodium and trisodium phosphates. The employment of some of them in soap has been patented.

ILLUSTRATIVE CASES

ABUSE OF SOAP

CASE 1.—An employee in the laundry of a hospital, in order to avoid contracting some disease (?), washed his hands each time he handled soiled dry linen. He estimated he washed his hands twenty-five to thirty times a day with the soap used in the laundry. He informed us that he could work with canvas gloves and could wear protective sleeves.

CASE 2.—An employee in a dye house informed us that he, as well as the other employees, washed their hands with the soft soap used in their shop to scour wool.

CASE 3.—A woman employed in making desk pads experienced a dermatitis of both hands. She glued leather on linoleum. On account of the glue adhering to her hands, she immersed them in a basin containing soap and water about a hundred times daily. She has been doing the same work for three years.

TURPENTINE AND KEROSENE TO CLEANSE HANDS

CASE 4.—A woman in a printing shop used turpentine and kerosene for many years in order to remove stains from her hands and forearms. We treated her for dermatitis involving these areas. A patch test with turpentine gave a positive reaction.

PAINT SOLVENT TO CLEANSE HANDS

CASE 5.—A workman spraying lacquer on furniture with a squirt gun presented dermatitis on the hands and forearms. To remove lacquer from his hands and forearms he has employed paint solvent for four years.

70. Orris root is an allergenic substance.

SCOURING POWDER TO CLEANSE HANDS

CASE 6.—An employee in a hat factory presented dermatitis on both hands. He handled dyed hats which stained his hands. For three years he had removed such stains by using a scouring powder. All his fellow-workers used this powder, which they obtained from the janitor, who used it to clean lavatories.

CASE 7.—A man employed in a carpet factory to clean looms presented acute dermatitis on the hands and arms. In order to remove grease, he washed with a scouring powder which was used to scrub floors. The dermatitis appeared after the initial use of this powder.

CALCIUM HYPOCHLORITE TO REMOVE DYE

CASE 8.—An employee in a dye house presented dermatitis on the hands and forearms. For twenty-five years he had been handling dyes. He washed his hands about twenty times a day, using an abrasive soap and also the soap used to wash yarn. To remove stains from his hands about three times weekly he used a solution of calcium hypochlorite (hypochlorite of lime) employed in his work.

ONE USE OF GLOVES

CASE 9.—In a tannery girls were employed applying "seasoning" by hand. Some used a brush; others, a rag. Gloves were worn only when the seasoning contained dye and then only to prevent the finger nails from being stained. The wearing of gloves was satisfactory. "Seasoning" used on finished skins contains water, mineral pigment, blood albumin, casein, castor oil, formaldehyde as a preservative and at times dyestuff.

IMPROVISED PROTECTIVE SLEEVES

CASE 10.—An employee in a tannery told us that he and his fellow-workers on their own initiative used discarded inner tubes of automobile tires as protective sleeves.

PINE TAR AND AXLE GREASE

CASE 11.—In a tannery the men known as "beamers" applied pine tar and axle grease to their hands before working. The work involved trimming wet delimed pelts with a knife on a wooden beam. The skin of the fingers of these men was white, puckered and considerably macerated. The reason given for the use of pine tar was as a protection against lime. It had been thus employed in that shop, according to the oldest employee, for fifty years. Axle grease was used to waterproof the skin. The use of pine tar to dry the fingers, permitting a better grasp of the knife handle, appeared to us to be a better explanation.

A SIMPLE PROTECTIVE MEASURE AND PRACTICE

CASE 12.—The men spraying paint in a large manufacturing plant applied freely to the skin of the exposed parts, before working, cold cream supplied by the company. Goggles and respirators were also used. At the end of the work period paint literally covered the exposed skin and was easily removed by means of a clean cloth, also supplied by the company. The men stopped work ten minutes before the usual time in order to cleanse their skin.

RECOMMENDATIONS FOR A PROTECTIVE APPLICATION

CASE 13.—Employees in a candy factory experienced dermatitis of the arms, which was alleged to be an expression of an allergic reaction to flour. The men

involved handled large slabs of sticky candy which they inserted into a machine that cut and packaged it. Flour was sprinkled on the slab by hand. Considerable flour dust was created when the machines were cleaned. The appearance of the eruption (with follicular involvement) suggested a dust-borne irritant flour as the cause. Pending installation of a ventilator, the application of formula 7 on the arms before working was one of the recommendations we made. Protective applications had to be dry and nongreasy. The formula has now been used for seven months. The incidence of dermatitis following its use has been decreased.

RECOMMENDATIONS FOR A PROTECTIVE APPLICATION

CASE 14.—Dermatitis of the hands and forearms appeared among employees engaged in nickel-plating electric utensils. The men immersed a frame holding the utensils in a tank containing a steaming solution of a proprietary compound. The exact composition of this compound was not known, but it was thought to contain sodium hydroxide, trisodium phosphate, sodium carbonate and sulfonated alcohol. The men worked with their sleeves rolled up and with their hands and arms exposed to the steam and mist from the solution. Dermatitis appeared after variable periods of exposure. Some employees, however, regardless of prolonged contact never had dermatitis. We determined by patch tests of normal persons (not employees) that the factor in question was a primary cutaneous irritant. It was not practical for the men to wear gloves, and we were informed that it was not possible (?) to ventilate the tank containing the solution. It was recommended that: (1) consideration be given to employing Negroes, (2) protective sleeves be worn,[71] (3) candidates for employment who gave a history of ever having eczema or who were blondes would not be appropriate for this work, (4) such men be employed who gave negative reactions to patch tests with the control substances used in patch tests and (5) protective applications to the skin be employed. Formulas 7 and 9 were suggested. Selection of the one to be used was to be made after a trial of each formula.

SUMMARY

The role of cleansing agents applied to the skin in causation of industrial dermatitis is discussed.

The results of studies of methods employed by workmen to cleanse their hands are presented. These studies emphasize the importance of mechanical devices in the prevention of industrial dermatitis and the need of education of workmen and others concerned in preventive measures, especially in the care of the skin and in harmless methods of cleansing it.

Protective medicinal applications to the skin (protective hand creams) in prevention of industrial dermatitis are discussed. Eight formulas of protective medicinal applications, comprising greasy and nongreasy preparations and those that dry leaving a film are given.

Other protective applications (applied before working) are discussed. These essentially utilize (*a*) hydrous wool fat for protecting

71. Those of the type known as leatherettes (Milburn Manufacturing Company, Detroit) were recommended.

from the carcinogenic action of mineral oils and tars, (*b*) different applications to prevent dermatoses from petroleum and lubricating oils, (*c*) bland oils to facilitate removal of paint, ink and dirt and (*d*) sodium bisulfite ($NaHSO_3$) as a neutralizing and reducing agent.

Harmful and harmless methods of cleansing the skin are discussed. A 10 to 30 per cent solution of sodium hyposulfite and a 0.5 per cent solution of sodium metasilicate are stressed as harmless agents for removing such substances as paint, ink and dye and as general cleansers.

A formula consisting of a mixture of sulfonated neat's foot oil, liquid petrolatum and corn meal is given as a substitute for mechanic abrasive soap.

The action of soap on the skin is discussed, including mechanic soap and its ingredients, toilet soap, neutral soap, soaps for household and laundry purposes, soap fillers, silicates of sodium, the allergenic action of soap and soap as a primary cutaneous irritant. Soap is not sufficiently soluble, as employed for toilet or laundry purposes, to permit the alkaline salts it contains, especially sodium carbonate, in sufficient concentration in soap solution to act as cutaneous irritants. Exceptions are soaps in powder form mixed with sodium carbonate.

Detergents other than soap are discussed: triethanolamine soap, naphthenic acid soap and sulfonated oils. Formulas of different combinations of sulfonated olive oil, sulfonated neat's foot oil, gelatin and liquid petrolatum and one containing sodium lauryl sulfate are proposed as soap substitutes. Sulfonated esters, sulfonated ethers and sulfonated alcohols as cutaneous detergents are discussed, as are certain vegetable meals and a variety of minerals.

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1934 Spruce Street.
1801 Pine Street.

ABSTRACT OF DISCUSSION

DR. EARL D. OSBORNE, Buffalo: Dr. Klauder and his collaborators have presented a great deal of material of practical value to dermatologists handling cases of industrial dermatitis. I am sorry they did not have time to say more about sulfonated oils, sulfonated alcohols and aryl alcohols now appearing on the market.

The first problem in the prevention of industrial dermatitis is the prevention of contacts with irritants and sensitizing substances handled in industry. I agree that in the majority of cases industrial dermatitis is due to the use of various cleansing agents rather than to specific substances used in industry. It is therefore essential that dermatologists should prescribe and compound suitable preparations that workmen can apply to prevent contact with irritants and sensitizing substances. They should also advise the use of nonirritating cleansing agents, such as Dr. Klauder and his co-workers have enumerated, rather than the strong alkaline and abrasive substances now in use. In addition to various substances

which these authors have already mentioned, there is one other simple preparation of great value in the prevention of industrial dermatitis and that is paraffin ointment B. P., which consists of 3 per cent yellow wax (beeswax) and 20 per cent hard paraffin in petrolatum. This is a white, relatively nongreasy preparation and should be applied three or four times during the working day. In those industries requiring the application of an impervious material to prevent contact with certain substances, a base consisting of 20 per cent glyceryl monostearate, 5 per cent glycerin and 5 per cent spermaceti in distilled water and incorporating from 10 to 20 per cent of zinc oxide or some other impervious material offers an excellent nongreasy protective preparation.

In the line of cleansing agents, the new sulfonated oil recommended by Dr. Blank [64] is a good preparation. The suggestion of Dr. Klauder and his co-workers regarding the incorporation of cornmeal is excellent. At the present time my associates and I are in the midst of testing with sulfonated oil and sulfonated alcohol a large group of persons with normal skins and another series of persons who have various types of dermatitis. To date, we have tested approximately 100 persons with normal skins with the sulfonated oil mixture just mentioned, with negative results. Of a group of 100 persons who had a preexisting or coexisting dermatitis, there were 2 with positive reactions. So far we have seen no exaggeration of an industrial dermatitis from the use of sulfonated oil as a cleansing agent. Recently, we have been experimenting with sulfonated lauric alcohol, which can be easily made into cake form and is therefore much more practical than a liquid oil preparation. We have tested 30 persons having some sort of a dermatitis with this preparation, with two strongly positive reactions. Sodium aryl sulfate is another new substance which has been used commercially in the textile industry for its detergent quality and is similar to sulfonated lauric alcohol. To date, we have had one severe reaction from this substance. It is therefore evident from our experience that so far the sulfonated oils in Dr. Blank's mixture (olive and tea-seed oils) are satisfactory, with only a slight chance of the production of a dermatitis in persons who have had a preexisting dermatitis, whereas the use of sulfonated lauric alcohol and sodium aryl sulfate by such persons may be attended with considerable danger of the production of a severe dermatitis.

Dr. C. Guy Lane, Boston: I was much interested in Dr. Klauder and his co-workers' classification of these cleansing agents which have a degreasing effect and also in their classification of the preparations they have been working on. These classifications will be of great help not only in industrial work but in other types of dermatologic work. I subscribe wholeheartedly to all that they said with regard to safety engineers. Such engineers have a far better conception of preventive measures dealing not only with general industrial hazards but with dermatologic conditions in industry than the average industrial physician or surgeon working in large or small plants part or full time. I was glad to hear Dr. Klauder and his associates emphasize the necessity of education in this subject, not only education in the care to be employed in the selection of materials to be used and in the method of using them but education of workers in the use of these materials as prescribed by the safety engineer or by the particular firm. I have been interested in watching the work of Dr. Blank on this subject. Dr. Klauder and his associates have already reviewed the two phases of his work: first, with reference to fatty acids and varying p_H concentrations on the skin and, second, with reference to the use of sulfonated oil compounds as detergents. These can be used by persons who are sensitive to soaps which contain alkali. Work is now

under way to develop a preparation for the use of certain surgeons who have a sensitivity to soap. One criticism of sulfonated oil has been that it has a drying effect. I was much interested in the fact that Dr. Klauder and his associates recommend elimination of the water entirely in sulfonated oil preparations and prefer using a high percentage of oil and the addition of corn meal, which should be an improvement.

Dr. Hiram E. Miller, San Francisco: I should like to ask Dr. Klauder whether he has used protective creams in routine dermatologic practice. The protection of preexisting lesions of the skin is of value in some instances.

Dr. Joseph V. Klauder, Philadelphia: I do not believe that the dermatologic investigation of detergents has followed the progress made in industrial detergents. There is need for chemical investigation to provide better methods of cleansing the soiled hands of workmen. I doubt if any chemist has given thought to this. My co-workers and I discussed a number of detergents, especially silicates of sodium. Sodium silicate is an important detergent used in industry. I do not believe that there has as yet been sufficient investigation of the sulfonated esters, ethers and alcohols as cutaneous detergents. The German preparation "praecutan" belongs in this group and is to my knowledge the only one that is commercially available. I hope our paper will serve as a plea for greater attention to the matter of cutaneous detergents and for investigation of methods to remove grease, stain and other material from the skin. In answer to Dr. Miller, we have sometimes used protective applications when treating patients with eczema, and I think that such applications have been effective.

PEMPHIGUS

EXPERIMENTAL STUDIES ON THIRTY-FOUR PATIENTS

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AND
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This communication is a summary of certain data obtained from the study of 34 patients with pemphigus. All the patients were admitted to the outpatient department or to the wards of the Massachusetts General Hospital between 1935 and 1939, inclusive. The ages varied from 4 to 76. There were 19 men and 15 women. The nomenclature of the types of pemphigus which we have used and will retain in this discussion varies somewhat from that in contemporary textbooks. The pemphigus in our patients has been classified simply as acute or chronic.

The acute form may be distinguished clinically by the early development of lesions in the mouth, a rapid, fulminating course, racial susceptibility (8 of the 10 patients with acute pemphigus in our series were Jews) and a high incidence in the fourth and fifth decades of life. Further, this form may be distinguished chemically by certain abnormalities in the acid-base balance of the blood. Chronic pemphigus, on the other hand, progresses slowly and may have prolonged asymptomatic periods. If lesions develop in the mouth they do so late in the course of the disease. There appears to be no characteristic racial distribution. The patients tend to be older than those with acute pemphigus. Death occurs from a disease other than pemphigus. The chemical constituents of the blood generally are within the average range for normal persons. In the group to be discussed acute pemphigus was diagnosed in 10 patients and chronic pemphigus in 24 patients.

It seems particularly desirable to emphasize that the patients with acute pemphigus were not suffering from the disease known as malignant

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From the Medical and Dermatological Clinics of the Massachusetts General Hospital and the Fatigue Laboratory, Harvard University.

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The following persons assisted in this study: Dr. C. G. Lane, Dr. J. H. Swartz, Dr. W. Lever, Dr. J. Lerman, Mr. William V. Consolazio, Mr. L. J. Pecora and Miss E. Thorogood.

or acute butcher's pemphigus. During the period of this study it is believed that we did not see any patients with butcher's pemphigus, nor was the diagnosis considered seriously in any case.

The cause of pemphigus is unknown, although various investigators have attempted to implicate bacteria and viruses. A critical appraisal of several studies finds the question still unanswered. Concerning the pathogenesis, however, there is some agreement, and acceptable evidence indicates that pemphigus is intimately associated with one or more metabolic disturbances. As early as 1906 Cassaët and Micheleau [1] suggested a dysfunction of water and salt metabolism in patients with this dyscrasia. Baumm,[2] Stümpke,[3] Urbach,[4] Kartamischev [5] and others have confirmed the observations. Many of the conclusions, however, were based on assumptions and were not derived from experiments. Recent improvements in the methods for determination of concentrations of acid-base constituents in biologic material and volume of body fluids have enabled us to complement previous observations.

The division of our observations into several categories is arbitrary but convenient for presentation. The abnormalities in the concentrations of the constituents of the blood are greater in patients with acute pemphigus than in those with chronic pemphigus. They will be discussed separately. The changes in body fluid volumes are similar for the two forms of pemphigus. They will be discussed together. A short presentation of the postmortem observations on 6 patients will follow. Specific therapeutic procedures were employed for 5 patients with acute pemphigus. An inducement of remissions is believed to have been achieved. Deductions concerning causation will conclude the presentation.

The concentrations of electrolyte and nonelectrolyte constituents in the arterial serum of a normal person are: sodium, 140 milliequivalents per liter; potassium, 4.5 milliequivalents per liter; calcium, 5 milliequivalents per liter; magnesium, 1.5 milliequivalents per liter; chloride, 104 milliequivalents per liter; bicarbonate, 25 milliequivalents per liter; protein, 7 Gm. per hundred cubic centimeters; phosphate, 4 mg. per hundred cubic centimeters, and nonprotein nitrogen, 30 mg. per hundred cubic centimeters. The sum of sodium, potassium, calcium and mag-

1. Cassaët, E., and Micheleau, E.: Sur deux cas de pemphigus traités par la déchloruvration, Arch. gén. de méd. **1**:129, 1906.

2. Baumm, G.: Ein Beitrag zum Kochsalzstoffwechsel bei Pemphigus, Arch. f. Dermat. u. Syph. **100**:105, 1910.

3. Stümpke, G.: Liegen beim Pemphigus Störungen der Kochsalzausscheidung vor? Arch. f. Dermat. u. Syph. **108**:467, 1911.

4. Urbach, E.: Zur Pathochemie des Pemphigus, Arch. f. Dermat. u. Syph. **150**:52, 1926.

5. Kartamischev, A.: Ueber die Oedembereitschaft bei Pemphigus vegetans, Arch. f. Dermat. u. Syph. **143**:184, 1923.

nesium constitutes what is known as total fixed base. There is no comparable expression in current use for the sum of the acids. The sum of the acids must approximately equal the sum of the bases, however, as serum is essentially neutral in reaction. Of the constituents just enumerated, we are especially interested in this study in sodium, potassium, calcium, total fixed base, protein and nonprotein nitrogen.

The methods for the analysis of the constituents of the blood have been described.[6] Blood and plasma volumes were determined with the photocolorimeter by the method of Gibson and Evans.[7] Interstitial fluid volumes were determined by the method of Crandall and Anderson.[8]

The concentration of serum sodium in all the patients with acute pemphigus was less than 132 milliequivalents per liter in one or more samples of serum (charts 1 and 2) which were studied during the period when oral lesions were present. Three patients with acute pemphigus shortly before death had a serum sodium concentration of approximately 120 milliequivalents per liter. These values are indicative of a profound disturbance of salt metabolism, such as may be observed in advanced chronic nephritis, diabetic coma, adrenal insufficiency or severe heat cramps. The deviation from the normal of this constituent in patients with pemphigus was associated with the severity of the clinical condition and with the mass of skin involved. Similarly, a return toward normal of the concentration of serum sodium was associated with clinical improvement and regression of cutaneous lesions. Exceptions were noted shortly before death in 2 patients who had been under observation for several months. Each had experienced at least one clinical remission with restoration of a normal concentration of serum sodium. Late in the course of the illness the serum concentrations were normal, although the clinical state was ominous.

The concentrations of total fixed base and potassium were not determined prior to 1937. Three patients with acute pemphigus studied since that time have had at most determinations a concomitant lowering of total fixed base and sodium. Exceptions were noted when changes in serum sodium were accompanied by an increase in serum potassium. The highest concentration observed in serum potassium was 12.7 milliequivalents per liter. After active treatment this value decreased to 4.9 milliequivalents per liter one week later. A subsequent return to

6. Talbott, J. H.: The Interpretation of Clinical Chemical Procedures, Ohio State M. J. **35**:137, 1939.

7. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of Blood Volume: Clinical Application of Method Employing Azo Dye "Evans Blue" and Spectrophotometer, J. Clin. Investigation **16**:301, 1937.

8. Crandall, L. A., Jr., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate, Am. J. Digest. Dis. & Nutrition **1**:126, 1934.

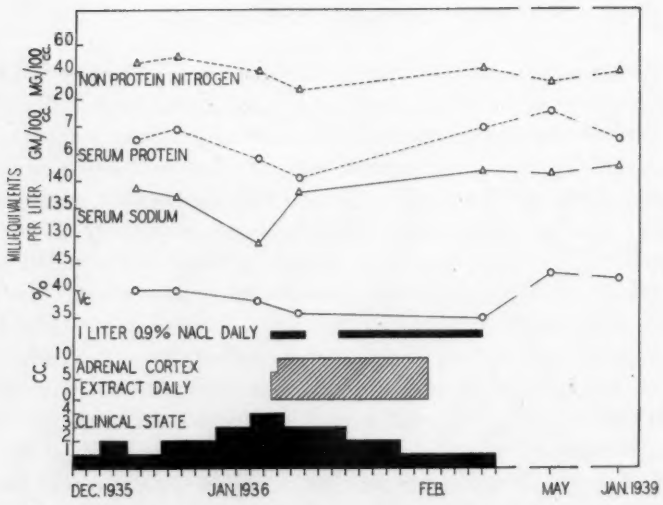

Chart 1.—Experimental observations and treatment of a patient with acute pemphigus who experienced an induced remission which has persisted for more than three years.

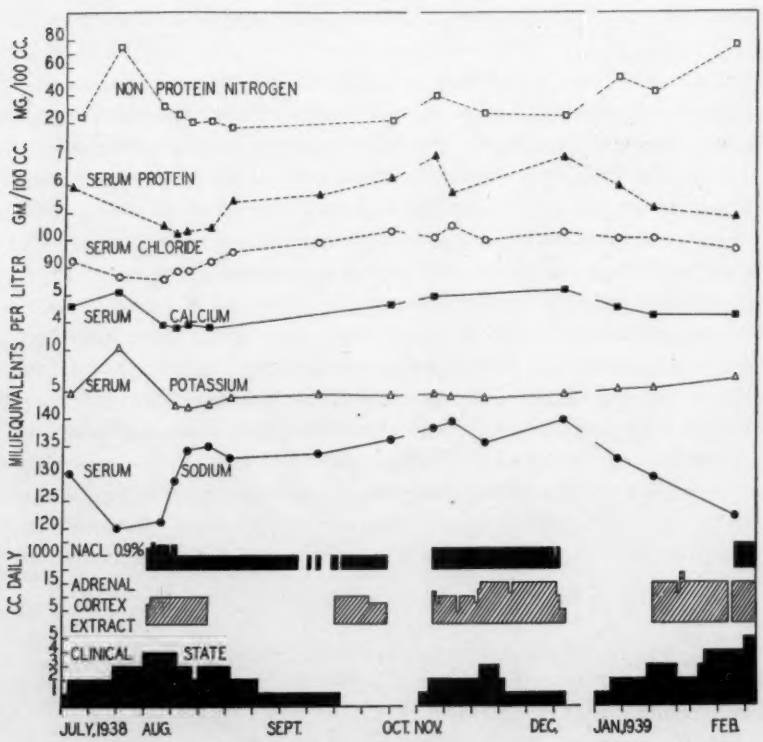

Chart 2.—Experimental observations and treatment of a patient with acute pemphigus who experienced two induced remissions and subsequently died. (A scale of 0 to 5 is used to represent the clinical state; 0 implies no local or general symptoms. Death occurred early in February 1939.)

11.9 milliequivalents per liter was accompanied by exacerbation of cutaneous lesions.

The concentration of serum calcium was diminished during a relapse in all the patients with active pemphigus in whom it was investigated. There did not appear to be a constant correlation between the level of this constituent and the clinical condition. In 3 patients it was less than 4 milliequivalents per liter for two or more weeks. In each a return toward normal followed whole blood transfusions and was not related chronologically to clinical improvement. An abnormal concentration of calcium was accompanied invariably by a diminution in concentration of serum protein. It is assumed, therefore, that the principal reduction was in the calcium bound to protein and that the concentration of ionized calcium was not appreciably altered.

The serum protein concentration was less than 5.2 Gm. per hundred cubic centimeters at least once in each patient studied. Restoration followed transfusions of whole blood when these were given. A progressive decrease with each successive relapse was characteristic. In 2 patients improvement in the clinical state was followed by restoration of protein concentration without transfusions. The concentration of serum albumin and globulin and the albumin-globulin ratio were determined in several samples of serum. A decrease in concentration of albumin with an increase in concentration of serum globulin was observed. The resulting ratios (0.6 to 1.4) were in the range noted in patients with lipoid nephrosis and edema.

The concentration of nonprotein nitrogen in the serum was normal in 2 patients and elevated in 5. The highest value observed was 75 mg. per hundred cubic centimeters. During periods of clinical improvement a return toward normal was noted.

Patients with chronic pemphigus showed abnormal concentrations of constituents in the blood less frequently; the variations from normal were quantitatively smaller. Only 6 of the 24 patients in this group had a serum sodium concentration below 135 milliequivalents per liter; the lowest observed was 131. This minimal value for patients with chronic pemphigus is similar to the maximal value for patients with acute pemphigus. Determinations of the constituents of the serum were not made frequently, but the available data suggested that the mass of skin involved was not related directly to the changes in the concentration of serum sodium. Likewise there appeared to be no correlation between the level of serum sodium and the course of chronic pemphigus.

The concentration of potassium was determined in the serum of 10 patients with chronic pemphigus. The amount was above normal in only 1 sample of serum (8.2 milliequivalents per liter). The concentration of calcium was 4.5 milliequivalents per liter or less in the serum of 8 of the 9 patients for whom determinations were made; the lowest value

observed was 4 milliequivalents. The serum protein concentration was determined for 17 patients and in 7 specimens was found to be less than 5.5 Gm. per hundred cubic centimeters. It was observed in cases of acute pemphigus that a diminution in concentration of serum protein was accompanied by a diminution in concentration of serum calcium. The concentration of nonprotein nitrogen was above 40 mg. per hundred cubic centimeters in the serum of 4 patients, all of whom were older than 65. It is reasonable to attribute the changes to age rather than to associate them with the pathogenesis of the cutaneous lesions.

For control observations determinations were made of the acid-base balance of the blood of 9 patients with generalized eruptions other than

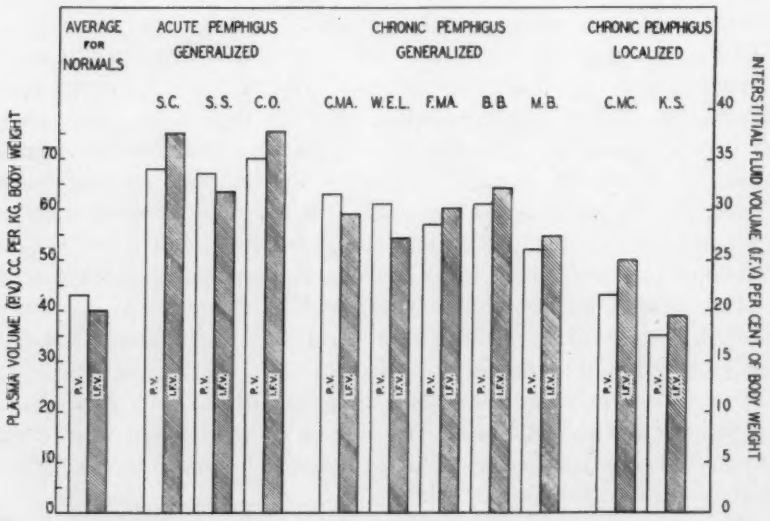

Chart 3.—Observations of plasma and interstitial fluid volumes of patients with either acute or chronic pemphigus.

pemphigus. The abnormal concentrations in this miscellaneous group of patients were not considered significant. It is believed, therefore, that the changes in concentration of sodium, potassium, total fixed base, calcium, protein and nonprotein nitrogen observed in the blood of patients with acute pemphigus are noteworthy.

Plasma volume, blood volume and interstitial fluid volume (chart 3) were determined for 3 patients with acute pemphigus and for 8 patients with chronic pemphigus. All patients with generalized cutaneous lesions had an increase above normal in the determined values. During the critical stage of acute pemphigus the plasma volume determinations showed increases as great as 60 per cent above the average for normal persons. Absolute changes in interstitial fluid volume were greater, although the percentile increase was less. Patients with acute pemphigus

had a 7 to 10 Kg. excess of fluid in the interstitial spaces. After recovery from acute pemphigus 1 patient had normal values for these constituents. There appeared to be no correlation between formation of bullae and increase in volume of body fluid.

Routine studies of the urine showed no evidence of renal dysfunction, such as might account for chemical changes in the blood and increase of interstitial fluid. The excretion of phenolsulfonphthalein was studied in 4 cases of acute pemphigus and in 6 cases of chronic pemphigus. A normal response was noted in most instances. Inulin and creatinine clearances were determined for a patient with acute pemphigus. Normal data were obtained. It is concluded that the metabolic changes in pemphigus may develop without glomerular or tubular dysfunction.

Necropsies on 3 patients with chronic pemphigus showed no recognized changes which contributed to our understanding of the pathogenesis of the disease. A serious complicating condition was noted in each instance. Necropsies on 3 patients with acute pemphigus, however, revealed changes which were believed to be significant. Two of the 3 patients had anatomic changes in the adrenal glands which were visible grossly and microscopically. One patient had infarction of one adrenal gland and hypertrophy of both. Both adrenal glands were hemorrhagic in the second patient. The other endocrine glands were normal in both groups of patients.

Our particular interest in treatment was confined to oral and parenteral therapy for patients with acute pemphigus. The acid-base changes in the blood were consistent with adrenal insufficiency. The anatomic changes in the adrenal glands of 2 patients who died with acute pemphigus appeared to confirm the pathogenesis of the chemical changes. Treatment was instituted, therefore, to correct the dysfunction. This consisted of administration of large amounts of adrenal cortex extract and sodium chloride solution parenterally. Each of the 5 patients treated with these substances had a restoration of the concentrations of sodium, potassium, total fixed base and nonprotein nitrogen. Clinical improvement followed the restoration. Neither the clinical improvement nor the changes in the serum were as rapid, however, as those which are observed in the treatment of uncomplicated acute adrenal insufficiency. In some cases more than a week elapsed before the development of new bullae had been checked. This suggests that factors other than adrenal insufficiency are important in the pathogenesis of acute pemphigus.

The duration of remission was variable and apparently unpredictable. Two patients had a satisfactory remission during the first admission to the hospital, which has continued for three and one-half and three years respectively. The other patients were less fortunate. As long as active treatment was continued, clinical improvement was noted. A relapse invariably followed cessation of treatment. Resumption of treat-

ment after one or more relapses eventually was ineffective. The duration of life after the first onset of generalized eruption in this group of 3 varied from four to eight months.

In contrast to the inducement of remissions in the 5 patients treated, a similar number not treated died promptly. The longest interval between onset of acute exfoliation and death was two months; the shortest interval was eleven days. None of the patients in this group enjoyed a spontaneous remission, and once they had become chronically ill, the clinical course was one of uninterrupted regression.

Any contemporary theory of the cause of pemphigus is inadequate. The statement that pemphigus is a virus or bacterial disease is not supported as yet by acceptable evidence. If it is proved, however, that pemphigus is produced by a virus or a streptococcic infection, it would strengthen our argument concerning the pathogenesis and contribute toward a satisfactory explanation of the complete pathologic syndrome. It seems likely that infections reduce the amount of normally available adrenal cortex hormone. A micro-organism or an ultrafiltrable organism might produce the cutaneous lesions in acute pemphigus as well as impede the elaboration of the adrenal cortex hormone. If this interpretation is correct, the chemical and fluid changes in the body should be considered as secondary manifestations.

SUMMARY

Metabolic studies of 34 patients with pemphigus are reported. The patients were classified simply as having either acute or chronic pemphigus. Acute pemphigus is not to be confused with the syndrome known as malignant butcher's pemphigus. Studies of the blood of the patients with acute pemphigus showed changes in concentration of constituents consistent with adrenal insufficiency. Patients with either type of pemphigus showed an increase in volume of plasma, blood and interstitial fluid.

Five patients with acute pemphigus were given supportive treatment only. Death followed in from eleven days to eight weeks after onset of acute symptoms. Necropsies were performed on 3 patients, 2 of whom showed anatomic changes in the adrenal glands. The other 5 patients with acute pemphigus were given large amounts of adrenal cortex extract and sodium chloride solution. A remission followed in each patient. This persisted three and one-half and three years, respectively, in 2 patients without further specific treatment. In the remaining 3 patients, the remission persisted only as long as active material was administered, and eventually this became ineffective.

It is believed that no contribution to knowledge of the causation of the disease has been made. Our understanding of the pathogenesis, however, is believed to be enhanced.

ABSTRACT OF DISCUSSION

DR. RICHARD S. WEISS, St. Louis: Dr. Talbott has presented a study of pemphigus which is instructive and illuminating not only so far as the pathogenesis of the disease is concerned but also from the standpoint of treatment. In fact, his observations might lead one to believe that there is a modicum of renewed hope for the severely sick patients with acute pemphigus. Dr. Talbott does not claim that he has a new cure for pemphigus, but his studies indicate that we may have an additional method of treatment which materially increases the chances for recovery or remission.

It is interesting to note that there are changes in the concentration of several of the chemical constituents of the blood serum in certain cases of pemphigus. I am not an expert in blood chemistry and so cannot discuss the paper from the standpoint of variations in the concentration of the constituents of the blood serum with any great degree of accuracy. However, it appears that in some instances there was a profound disturbance of salt metabolism and water metabolism, such as is seen in patients with advanced chronic nephritis, diabetic coma and adrenal insufficiency; and when measures were taken to supply the body with those constituents of serum that were necessary to restore that fluid to approximately normal concentration, the improvement in a number of the patients was quite evident.

Dr. Talbott has demonstrated histologic changes in the adrenal glands of several of his patients at autopsy, and on this basis he has obtained remissions and improvement by treatment directed toward relief of adrenal insufficiency. If one can induce remissions in these patients with more or less acute pemphigus by the administration of physiologic solution of sodium chloride and adrenal cortex extract, it may be that the percentage of so-called cures will rise. Let it be emphasized, however, that these patients must be selected, that careful studies of blood chemistry must be made along the lines that Dr. Talbott has indicated and that this treatment should be given only to patients who present the apparent syndrome of adrenal insufficiency.

Dr. Talbott stated that clinical improvement eventually followed a restoration of the acid-base equilibrium in 5 patients but that neither the clinical improvement nor the restoration of the blood salts was as rapid as one observes in the acute crisis of Addison's disease. In fact, more than a week usually elapsed before the development of new bullae was checked. Therefore, he draws the conclusion that factors other than adrenal insufficiency are extremely important in the pathogenesis of foliaceous pemphigus. I think it is important to emphasize that they make no claim that acute adrenal insufficiency is the sole etiologic mechanism.

It seems to me that Dr. Talbott has checked and guarded his experiments by showing that exacerbations occurred when the treatment was discontinued. He has apparently demonstrated that there was a diminution in the concentration of serum sodium in certain cases of pemphigus foliaceus and that there was a decrease in the total fixed bases (the chlorides and proteins) and an increase in the concentration of potassium and nonprotein nitrogen. A definite disturbance of volume changes in the body fluid was apparently demonstrated; therefore, improvement or remissions may be expected in a certain number of patients if treated on the basis of adrenal insufficiency. I hope that others may have the opportunity to make similar studies, so that Dr. Talbott's observations may be confirmed in a very large series. At any rate, I believe that even this small series has given an accessory treatment for use in certain cases that may prove very valuable.

DR. C. GUY LANE, Boston: There is always a question of the classification of pemphigus. In my opinion, Dr. Talbott has done right in classifying these patients

as having acute pemphigus or chronic pemphigus. Whether one thinks of the disease as an acute fulminating type or as a more benign type lasting longer or perhaps divides it into types such as pemphigus vulgaris and pemphigus foliaceus, one can still observe, and perhaps more correctly, the classification which the authors have adopted for the present discussion. There is not yet any satisfactory etiologic classification, but there is beginning to be the suggestion of a classification, perhaps as a result of therapy. For example, consider further the two groups of patients with acute pemphigus, those who were untreated and died within a comparatively short time and those who, with therapy carried on in accordance with the chemical findings, had remissions coincident with treatment but eventually did not respond. Here is a possibility of grouping certain patients with the acute form of the disease by their response to therapy. Another group includes those who respond to the Davis treatment, and then there are a few patients who have also responded after treatment with dihydrotachysterol.

It has been interesting to watch the subsiding of cutaneous involvement as treatment has progressed; to see the less frequent appearance of bullae and eroded areas, a gradual improvement in the general condition of the patient, finally only scarring and pigmentation and eventually complete recovery. It has been a most striking clinical picture as the treatment has progressed.

It seems possible that this work may indicate another type or another subdivision of what is at present called pemphigus, resulting perhaps from organic manifestations similar to those discovered in the adrenal glands.

I said there is no satisfactory theory with regard to the origin of pemphigus, and perhaps it is dangerous to propose one. At the same time, let me review some of the ideas which have been mentioned in the last few years. The Pels-Macht test has given a certain amount of information and indicates perhaps an influence by a toxin in the blood. The Ashton Welsh test also shows evidence of a toxic factor, indicated by the speed of streptococci in responding to electric current. These two suggestions indicate the possibility of streptococcic involvement. There have been a few cases reported in which improvement followed the administration of sulfanilamide, but these results have not been consistent.

It is a known fact that large bullous lesions are produced on the skin in impetigo and erysipelas. Again, perhaps this indicates a relation to the streptococci. Perhaps the correct theory of the cause of pemphigus has not been advanced; but I think Dr. Talbott has given definite aid in the diagnosis, classification and treatment of a certain type.

Dr. M. F. Engman, St. Louis: This type of work is much needed not only in the study of pemphigus but in the study of many diseases. It is a new kind of approach to these problems.

My associates and I have been interested in certain chemical studies too. Dr. Ross MacCardle has been working at the Barnard Free Skin and Cancer Hospital with microincineration and spectrographic studies of minerals in the skin. He has been studying normal subjects of different ages and is beginning to get a picture of the normal skin at various ages. He has observed, for instance, that the amount of silicon seems to decrease with age. Curiously, in the skin of some patients with pemphigus he noticed a marked increase in silicon. These patients were elderly, and it was remarkable to find a greater amount of silicon than that normal for that time of life. This, of course, is a preliminary observation, and no conclusions may be drawn from such isolated instances.

Dr. M. B. Sulzberger, New York: At the suggestion of Dr. Joseph Goodman, of Boston, I asked Dr. Talbott for the details of his treatment consisting of the

administration of adrenal cortex extract and saline solution. I had a patient with what seemed to be acute pemphigus. Unfortunately there was no beneficial effect from the treatment. I was unable to study the blood chemistry or to study the tissue fluids or blood plasma. However, I followed the treatment that he had outlined as closely as I could. The patient died about nine to ten weeks after the onset of acute symptoms. If one assumes that I treated my patient the way Dr. Talbott has treated his patient, and if one further assumes that my patient had the same condition as did those Dr. Talbott treated with the combination of adrenal cortex and salt solution, then the result in my case must be regarded as a failure of the method. However, totaling Dr. Talbott's results with mine gives 5 good results out of 6 trials, and that is still a very impressive figure in acute pemphigus. I hope that results continue in that proportion. However, I think that dermatologists must somewhat revise their ideas concerning the prognosis of pemphigus in general. One continually sees, hears and reads of new instances of isolated patients with pemphigus getting well with various forms of therapy. I think today one must say that while the prognosis of pemphigus is bad, it is not hopeless. Some patients with true pemphigus recover; and this seems to be true in younger persons and particularly in native Americans.

Dr. Theodore Cornbleet, Chicago: I observed a low store of vitamin C in patients with pemphigus. Because of this observation I gave this vitamin to these patients and found that it had supportive value. The patients apparently were buoyed up and stimulated by such treatment. Soon after the patients received sufficiently large amounts of vitamin C, the characteristic, offensive fetor emitted by persons with pemphigus was decreased or abolished. I found this fact of value in obtaining improved nursing care for them. This form of therapy does not alter the eventual course of the disease, because the patients die anyhow.

Dr. John H. Talbott, Boston: I appreciate Dr. Sulzberger's follow-up report on the patient who was treated with adrenal cortex extract later in the disease. It appears from the investigations made by my associates and me that the patients with acute pemphigus who respond are those treated early. The 2 patients with this form of pemphigus that are now alive, more than three years after their acute illness, were seen early in the disease. The chemical studies were completed and treatment was instituted before they had become gravely ill.

The matter of classifying the various forms of pemphigus is not settled, nor will it be easy for the majority of observers to agree on any one system of classification. We believe that our classification has merit because it is based on chemical abnormalities and clinical findings. It might be of interest to mention that during the past five years we have seen at least 4 patients with generalized exfoliation who would have been considered to have an acute form of the disease if the clinical course only had been considered. Abnormal concentrations of serum electrolytes were not observed in these patients, however, and we treated them for chronic pemphigus. Their subsequent course justified this presumption.

I shall refer briefly to some negative results we have obtained with various purified vitamins. More than four years ago we employed large amounts of vitamin C orally and parenterally in 2 patients with acute pemphigus and in at least 1 with chronic pemphigus. It was concluded at that time that the effect was negligible. Recently we used thiamin chloride, nicotinic acid and riboflavin, as well as vitamin C, with apparently similar results. It is possible that we did not use sufficient amounts for a sufficient length of time, but judging from the amounts necessary for therapeutic benefit in cases of known avitaminosis, adequate quantities were given.

TREATMENT OF RINGWORM OF THE SCALP WITH GENTIAN VIOLET

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AND

M. B. JOHN, M.A.

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Treatment of tinea with a fungicidal dye was suggested some years ago by Castellani,[1] who painted carbolfuchsin in ringworms of the foot and of the groin. For lesions secondarily infected or moist, he recommended this rather than methods of treatment in common use.

Dyes do not have as powerful fungicidal as bactericidal property. Farley[2] found that dermatophytes tolerated greater concentrations of gentian violet than bacteria and used the dye in his mediums for the isolation of fungi, to retard bacterial contamination. Cultures of various microsporons and trichophytons on Sabouraud's agar withstood concentrations varying from 1:166,000 to 1:41,000. Of the several dyes that may be used, neither fuchsin nor gentian violet is the most strongly inhibitive to fungus growth. With concentrations similar to Farley's, Leonian[3] found the restraint erratic, owing to technical variations, but definitely greater with malachite green than with gentian (crystal) violet.

McCrea's[4] cultures of trichophytons and epidermophytons were inhibited by brilliant green but not by gentian violet or basic fuchsin

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Read before the Section on Dermatology and Syphilology at the Ninetieth Annual Session of the American Medical Association, St. Louis, May 17, 1939.

1. Castellani, A.: (*a*) Carbol Fuchsin Paint in the Treatment of Certain Cases of Epidermophytosis, Am. Med. **23**:351, 1928; (*b*) Further Observations on the Treatment of Epidermophytosis of Toes and Certain Other Forms of Epidermophytosis by a Fuchsin Paint, J. Trop. Med. **32**:77, 1929.

2. Farley, D. L.: Use of Gentian-Violet as a Restrainer in the Isolation of Pathogenic Molds, Arch. Dermat. & Syph. **2**:459 (Oct.) 1920.

3. Leonian, L. H.: Effect of Position of Inoculum on Growth of Some Trichophytons in the Presence of Dyes, Arch. Dermat. & Syph. **25**:1016 (June) 1932.

4. McCrea, A.: Fungicidal Value of Some Common Dyes Against Dermatophytic Fungi, Mycologia **26**:449, 1934.

in equivalent concentrations. On the other hand, Schamberg and Kolmer [5] found that while brilliant green was the best restrainer of growth, the violet dye was superior as a fungicide.

FORMULA SELECTED

Our selection of a dye for the experimental treatment of tinea capitis rested less on in vitro fungicidal potency than on toleration of the dye by the tissue and effectiveness of the dye in the tissue. We employed concentrations a thousand times greater than those exhibiting differential fungistatic effect. We first tried, without success, a formula with bismuth violet, then newly reported [6] as effective in the treatment of wounds. Success had been widely acclaimed for gentian violet as an antiseptic for application to infected tissue, not only as a bactericide [7] but also as a parasiticide [8] and as a fungicide.[9] We adopted a formula consisting of 2 per cent gentian violet and 10 per cent salicylic acid in 95 per cent alcohol.

TREATMENT

The affected head was first shaved, cleared of all crusts with soap and water and then alcohol and painted with the gentian violet and salicylic acid solution. The treated area assumed a gaudy hue. This aspect of the treatment was found objectionable by Castellani in his treatment of epidermophytosis, though it was less so in our case, as the head remained covered to minimize contagion. Daily for a period of ten days the lesion was similarly scrubbed clean and painted. The medication caused crusts to form which tended to shield the lesion from further applications, and these crusts had to be removed. We attribute the better results obtained in private than in clinical patients to a more thorough preliminary cleansing; the former were treated by one of us, after preparation by a nurse, and the latter by medical students or by some one in the home.

RESULTS

Over three fourths of our patients were from the outpatient clinic of the University of Texas School of Medicine. As is expected of such a clientele, some did not cooperate well or return for the desired period

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5. Schamberg, J. F., and Kolmer, J. A.: Studies in the Chemotherapy of Fungus Infections, Arch. Dermat. & Syph. **6**:746 (Dec.) 1922.

6. Barksdale, I. S.: The Use of Bismuth Violet in the Prevention of Wound Infection, South. Med. & Surg. **91**:597, 1929.

7. Burke, V.; Jessup, M. P., and Philips, S.: Choice of Antiseptic Dye in Mixed Infection, J. Infect. Dis. **43**:131, 1928.

8. Faust, E. C.: Parasitical Potencies of the Tri-To Hepta-Methyl Derivatives of Rosanilin, Proc. Soc. Exper. Biol. & Med. **26**:748, 1929.

9. Gomez-Vega, P.: Mycostatic Studies on Certain Moniliae and Related Fungi, Arch. Dermat. & Syph. **32**:49 (July) 1935.

of treatment and observation, and cannot therefore be included in our report. In our opinion their response to the treatment, so far as it went, resembled that of the patients here reported on.

The effect has proved more satisfactory than that of other topical medications which we have employed. By "fully satisfactory effect" we mean a prompt response, with evident subsidence of clinical manifestations within two weeks and continued progress to complete recovery. Absence of evident response for a month is noted as unsatisfactory.

Our totals might suggest that ringworm of the scalp shows a fairly good response regardless of mycologic type. With 65 patients suffering from tinea capitis, we found a fully satisfactory response in 37 and a fairly satisfactory response in 10. We thought at first that the treatment was proving suitable for tinea capitis in general. The completed mycologic analysis shows, however, that the infections in our patients were due predominantly to microsporons of the animal type and that those due to microsporons of the human type or to trichophytons did not respond well. Microsporons of the animal type account for a much larger proportion of the cases of ringworm of the scalp in Galveston than reports indicate for some other localities. We read that in a majority of the instances cited by Ebert [10] microsporons causing the infections were of the human type; in a Montreal series [11] they were about equally of the animal and of the human type, and in an outbreak at Winnipeg [12] they were almost entirely of the human type. In contrast with this, in a series of 116 cases in Galveston in which the lesions yielded fungi infective to the scalp, we found Microsporum felineum (Microsporum lanosum) in 68 infections, Microsporum audouini in 16 and other species of Microsporum or Trichophyton in 32.

As the response of the respective mycologic types of ringworm has differed, we present our observations for each type separately.

Tinea Due to Microsporons of the Animal Type.—The most significant results were those in patients infected with microsporons of the animal type, the most common in our locality. Two thirds of the aforesaid 68 infections with M. felineum involved the scalp (others the face and neck and occasionally the extremities or trunk), and 30 of them, all in children, were treated with the gentian violet and salicylic acid preparation and were under observation long enough to show the result.

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10. Ebert, M. H.: Ringworm of the Scalp, M. Clin. North America **19**:1241, 1936.

11. Burgess, J. F.: Fungus Infection of the Skin: A Cultural Study of the Flora of Ringworm, Arch. Dermat. & Syph. **12**:853 (Dec.) 1925.

12. Davidson, A. M.; Gregory, P. H., and Birt, A. R.: Treatment of Ringworm of the Scalp by Thallium Acetate and the Detection of Carriers by the Fluorescence Test, Canad. M. A. J. **30**:620, 1934.

The mycologic and clinical manifestations were in all respects typical and seemed representative of infections with the animal type anywhere. Colonies of M. felineum appeared within a few days on Sabouraud's insolation medium, first circular and radiating, and later developing a downy surface growth that became loosely woolly. All strains showed a yellow-orange color of the under surface and a diffusible yellow pigment. The fully developed colony, apart from pleomorphic changes, was roughly circular and several centimeters across, with a surface powdery at the center and woolly toward the periphery. Within a month pleomorphism set in; snow white mycelium appeared in downy tufts, spreading rapidly into a medallion or radial branching effect and eventually in many instances covering the entire colony.

Morphologically, there developed on lateral branches enormous numbers of large spindle-shaped macroconidia, thick walled and spiny, averaging about 75 microns in length and 15 to 20 microns in width and containing from three to twelve cells. There also were club-shaped microconidia about 5 by 2 microns. The mycelia structure was typical, with raquet segments. As cultures became pleomorphic, chlamydospores became abundant, while the macroconidia and later the microconidia decreased and finally disappeared.

The lesions were maculosquamous, irregularly circular and more often multiple than not. They usually measured from 0.5 to 2.5 cm. across, with some smaller and some much larger. Hairs within their bounds turned white and broke off. There was sometimes secondary infection, crusting or other inflammatory sign.

Of the 30 patients whose lesions were treated with our gentian violet formula, the response in 21 was prompt and fully satisfactory; in 3 others it was less prompt but fairly satisfactory. The lesions of the remaining 6 did not respond well; on 2 the treatment was continued for two or three months (on 1 with much eventual improvement), while on the other 4 another treatment was substituted after two weeks, when this one seemed a failure. The patients whose lesions did not react well were slightly younger than the others, averaging about 6 years of age as compared with 7 years for all patients observed. Their lesions did not differ significantly in grade, extent of spread, secondary infection, any clinical indication of severity or in mycologic findings.

Nearly all the patients with ringworm due to microsporons of the animal type that came to us during this period have been so managed, and we cannot compare them with controls otherwise treated. Most of those not handled in this manner were epilated. Those that received other local applications did not show as favorable results, on the average, but they were too few for us to make significant comparison. Recalling

our experience before instituting the gentian violet treatment, we regard this as distinctly the most successful topical medication we have ever employed.

Tinea Due to Microsporons of the Human Type.—We instituted the same treatment on a number of patients infected with M. audouini, but on only 5 did we continue it long enough for any extended observation. The response was unsatisfactory in all but 1, and that patient was 11 years old and nearing the usual age for spontaneous recovery. Of the 4 in whom the results were noted as unsatisfactory, after a number of weeks 2 showed a favorable response, 1 eventually had the treatment changed and 1 finally lapsed from treatment, uncured. As a rule, we changed early to other kinds of treatment, thinking it unfair to continue one that was evidently inferior.

Ringworm due to microsporons of the human type has been found refractory to other topical medications that are successful with the animal type, even when these have been continued for months. It requires instead epilation by roentgen rays or some other means.[13] The lesions produced by the animal type tend to heal spontaneously in time, whereas those caused by the human type do not undergo spontaneous cure except with approach to puberty. With some exceptions,[14] neither type affects the adult.

These few cases are admittedly inadequate to establish the presumed negative value, particularly as the human type of tinea in our locality is culturally atypical. We have seen colonies with the central button, radial grooves and other characteristics commonly described, but our more usual colony grows into a flat, even bordered circular disk, with a feltlike surface and a color ranging from white to buff, often with concentric rings of deeper shade. The resemblance is sufficient for identification as M. audouini. The colony grows more slowly than that of M. felineum, and the pleomorphism, so common in the latter species, occurs only exceptionally. The microscopic structure is similar except that macroconidia are rarely found and are smaller than those of M. felineum. The lesion produced by this organism does not differ in appearance from that already described for the animal type, and only by laboratory observations can we distinguish the one from the other.

Tinea Produced by Trichophyton.—The ringworms of the toe and groin, which Castellani [1a] reported as responsive to treatment with dye, were presumably trichophyton or epidermophyton infections. We watched the response to gentian violet treatment in a few cases of tinea

13. Wise, F., and Wolf, J.: The Pharmacopeia and the Physician: The Use of Dermal Parasiticides, J. A. M. A. **107**:1126 (Oct. 3) 1936.

14. Fox, H., and Fowlkes, R. W.: Ringworm of the Scalp in Adults, Arch. Dermat. & Syph. **11**:446 (April) 1925.

capitis due to trichophytons. These infections differed in appearance from those caused by the microsporons and somewhat among themselves. They frequently presented a more granular or gritlike form of scaling and were more widely disseminated over the scalp, without as definite localization in circumscribed patches. Hairs within the affected areas were not so uniformly discolored and broken.

From the literature we had little hope of success, especially with the endothrix species. Farley [2] found that a trichophyton could withstand greater concentration of gentian violet than either of the two microsporons, and Lewis [15] found that the endothrix is peculiarly resistant to fungicidal applications. Trichophyton violaceum has received more attention than the others. It caused most of the ringworm of the scalp in adults reported by Chen and Kurotchin [16] in Peiping. Lewis and Hopper [17] reported that the ringworm caused by trichophyton offered greater resistance to treatment than that due to either of the microsporons, even M. audouini, and had greater tendency to relapse after depilatory measures. The only case in which we recovered T. violaceum was that of a small child with kerion, a complicated lesion for which we employed other medicinal treatment as well as the application of gentian violet. The treatment was successful.

We had a number of patients with infection of the scalp caused by a variety of Trichophyton epilans and treated 10 by this method. Our strains had the characteristics usually recorded for Trichophyton cerebriforme. The colony began as a small puff, and as it spread convoluted folds developed, with irregular radial grooves toward the center and a border fringed with radial spines, largely submerged. Most of our potassium hydroxide mounts showed endothrix arrangement of arthrospores. Often the lesions seemed virulent, sometimes extensively disseminated and numerous and sometimes red and swollen, containing yellowish pustules. Infections elsewhere on the body had a similar inflammatory character, the localization on the scalp being rather exceptional. A prompt and satisfactory result was obtained in 4 of the 10 patients and a fair result in 2 others.

Infections by a few other trichophytons that localize occasionally in the scalp were so treated, though there were only 1 or 2 of each. The response most commonly obtained was one at first favorable but without progress to complete cure. The lesions were usually of the trichophyton

15. Lewis, G. M.: Curability, Without Depilatory Measures, of Infections Caused by Animal Microsporons, Am. J. M. Sc. **189**:364, 1935.

16. Chen, F. K., and Kurotchin, T. J.: Tinea of Scalp Among Adults in Peiping, Nat. M. J. China **17**:185, 1931.

17. Lewis, G. M., and Hopper, M. E.: Ringworm of the Scalp: Clinical and Experimental Studies in Types of Infection Resistant to Treatment, Arch. Dermat. & Syph. **35**:460 (March) 1937.

type, sometimes resembling localized and crusted seborrhoea sicca. Most of them seemed to react well until nearly cured; then they would show patches of renewed activity spreading within the affected area. In most instances the treatment was given up after this initial failure, but in 1 a more extended course was tried with eventual success.

While the gentian violet treatment in this limited number of patients with ringworm caused by trichophytons was not as a rule successful, we are encouraged to try it further. We hope that it may prove useful against certain of the trichophytons at least, perhaps in extended courses.

Fifteen additional patients were observed from whom we did not succeed in isolating a fungus. The lesions of 10 responded to the treatment in a fully satisfactory manner and those of 4 in a fairly satisfactory manner. It seems likely that a large proportion of these infections were caused by M. felineum, in which event such an outcome would be anticipated.

SUMMARY

A local application is presented for the treatment of tinea capitis, consisting of 2 per cent gentian violet and 10 per cent salicylic acid, dissolved in 95 per cent alcohol.

The preparation is recommended for ringworm due to microsporons of the animal type but not for that due to microsporons of the human type.

The limited results of the treatment of ringworm due to certain trichophytons were in some respects encouraging.

810 Strand.

ABSTRACT OF DISCUSSION

DR. LESLIE M. SMITH, El Paso, Texas: Physicians are always grateful for suggestions and formulas which offer promise of shortening the course of ringworm of the scalp. A few years ago roentgen ray epilation was the standard routine treatment for such infections regardless of the causative fungus. More extensive use of the culture tube has changed this. Investigators of the subject now know that infections caused by the so-called animal microsporons tend toward spontaneous cure. Dr. Spiller and his co-workers have shown that a large proportion of the cases of ringworm of the scalp seen in Galveston are cases of infection with animal microsporons. At the other end of Texas, eight or nine hundred miles away, and under different climatic conditions altogether, I think there is an even greater proportion of cases of infection with animal microsporons. My colleagues and I estimated that in well over 90 per cent of our cases of ringworm of the scalp the lesions were due to that microsporon of animal origin M. lanosum. I believe M. lanosum is identical with the organism Dr. Spiller classifies as M. felineum. We have not done roentgen ray epilation of the scalp for, I suppose, seven or eight years.

The formula which Dr. Spiller and his associates have suggested, containing a keratolytic agent and a fungicidal dye, would be beneficial in this type of infection, if any local application would. My own personal experience with this treatment, since Dr. Spiller told me of his results, has been too brief to allow

accurate judgment. We have treated a few patients according to Dr. Spiller's directions, and on the whole our results have been satisfactory. I expect to try it further.

I believe the value of any treatment in these cases is enhanced by early epilation of the infected area by means of forceps. It isn't necessary to epilate the entire scalp, as is done with roentgen rays, but a few hairs should be pulled out each day. This certainly facilitates the cure. It accomplishes the double purpose of ridding the scalp of the bulk of the infected material and of allowing better penetration of the fungicides into the follicles.

Any intensification of the inflammatory process in the lesion tends to hasten the detachment and consequent removal of the hair. This can be accomplished by the application of irritants, such as mercury and iodine in combination or alternately, and also in some cases by causing a focal reaction by injecting a concentrated microsporon antigen or culture filtrate. I have seen the reaction occur when the antigen or filtrate was injected subcutaneously into the arm. In other cases in which I haven't been able to accomplish this, I have injected the antigen or filtrate intracutaneously into the lesion and have had a flare-up. I think that in some cases this hastens epilation by intensifying the inflammatory process and aids in the cure.

It is well to keep in mind these various methods of treatment and to consider a combination of several methods in cases in which the infection proves resistant to routine application of the various formulas which have been used.

Dr. W. F. Spiller, Galveston, Texas: Dr. Smith mentioned the lanosum and the felineum. They are one and the same thing. We follow Dr. Emmons, who visited us a while, in the use of the term felineum.

Pulling out the hair is a good method, but it is quite a job, especially if the hair is not short, as there may be so many small lesions that they won't be seen. That is the reason I always have the heads shaved.

Dr. Smith spoke of extract. We have done a bit of work on extract of fungi, but of fungi of other parts of the body. For a while we thought there was some virtue in the treatment with extract, but I have been thoroughly convinced that there is none, with one exception: we do get some good results from treating monilia infections with an extract.

Clinical Notes

FISTULAS FROM DEAD TEETH SIMULATING DERMAL EPITHELIOMA

DOUGLASS W. MONTGOMERY, M.D., SAN FRANCISCO

Although rarely mentioned in differential diagnosis, the mouth of a fistula may so resemble a cutaneous cancer as to deceive one into treating it as such. The following cases illustrate this fact.

REPORT OF CASES

CASE 1.—Recently a man was referred to me for treatment for what was thought to be an intractable epithelioma of the chin, for which he had been previously treated unsuccessfully by another physician. At the bottom of a deep conical hollow at the tip of the chin, exactly in the place where a dimple frequently occurs, was a small ulcer resembling an epithelioma. The patient said that eight months previously it had swollen and had discharged a quantity of pus and that it had been growing larger and deeper ever since. This should have put me on the alert, but its appearance, its course and its long endurance seemed to leave no doubt of its nature. A small quantity of soft tissue resembling either granulation tissue or tissue found in epitheliomas was curetted out. The lesion was then cauterized with trichloroacetic acid and irradiated with heavily screened radium. All appeared well for a couple of weeks, and then the lesion reopened. While my associate Dr. Viecelli was examining it, he employed a probe and demonstrated a fistula leading upward and backward toward the front teeth, one of which, the left lower incisor, was found to be discolored and seemingly dead. The patient then informed us that this tooth had been injured when he was a child but that it had never troubled him. He was sent to an oral surgeon, who examined the tooth roentgenologically. It was found to be dead and was extracted. The fistula was then cleared out, and definite and prompt healing ensued.

CASE 2.—Shortly afterward an elderly woman was brought to the office to be treated for what appeared to be an epithelioma of the left buccolabial fold. It was a small persistent lesion with some induration and was situated in a seborrheic region particularly apt for epitheliomatous degeneration. With my former experience fresh in mind, I examined the teeth and found the upper left bicuspid dead and a fistula leading toward it. I have not seen the patient since, but the result of proper treatment was said to have been successful.

With a fistula emanating from dead bony structure, pouting of the orifice is a well known telltale symptom. In neither case was this present. Its absence was explained by the situation of the orifices: in the man's case, at the bottom of a deep recession in the chin, and in the woman's, in an unusually deep buccolabial fold, called by humanists "the line of sorrow."

CASE 3.—Pouting, however, was present and beautifully demonstrable in a little girl who was brought to me at nearly the same time as the other 2 patients. The lesion was a smooth, glistening, bright red, accurately delineated, hemispheric

papule, with a minute hole, not a mere depression, in its very top. It was situated on the anterior surface of the upper gum directly over the root of a discolored, dead-looking upper incisor. There was no doubt about the diagnosis and about the pouting in this case, and the patient's course, after extraction of the dead tooth, was the same as that of the other 2 patients.

COMMENT

The first patient, the man with the fistula opening at the tip of the chin, was by far the most interesting. That the tooth should remain without troubling for so many years and then assert itself by causing a fistula in such an unusual situation was most strange. Fortunately, I did not remove tissue for biopsy, which would have resulted in a prominent scar. As it is, he has a large, deep but rather attractive dimple.

That the condition deceived me reminds me of a saying by Anatole France, "Il faut être très sage, pour eschapper les pièges de la Nature" (One has to be very wise indeed to escape the traps set by Nature).

On finding such a lesion, definitely recognizing it as the mouth of a fistula and treating it as such, one must not be too confident, for, as MacKee and Cipollaro [1] stated, long-continued inflammatory processes not infrequently give rise to cancer. Also, according to Kummer and Lang,[2] epitheliomas arising from fistulas of the bone are not rare, as they were able to report 44 cases. Even with the elimination of the offending tooth and the clearing out of the fistula, a cancerous process may already have begun, which later may assert itself.

1. MacKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer: A Practical Monograph, New York, American Journal of Cancer, 1937, p. 85.

2. Kummer and Lang, cited in Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Vienna, Urban & Schwarzenberg, 1935, vol. 2, p. 859.

CHROMIDROSIS

Report of a Case

MAYNARD MURRAY, M.D., CINCINNATI

Chromidrosis is a disease of unknown cause characterized by the excretion of colored sweat. Various etiologic factors have been advanced, such as menstrual disorders,[1] absorption of pigment-producing materials [2] and local abnormalities of pigment production.[3] This disease is to be differentiated from pseudochromidrosis, which is usually caused by pigment-producing micro-organisms. In most of the reported cases the condition was localized; in the case here reported the condition was generalized. Another notable and interesting fact is that the tears of this patient also contained the pigment.

From the Department of Physiology, University of Cincinnati.

1. Barie, E.: Sur un cas de chromidrose jaune, cataméniale, alternant sur les deux mains, Ann. de dermat. et syph. **10**:937, 1889.

2. Le Roy de Méricourt, A.: Mémoire sur la chromhidrose, ou chromocrinie cutanée, Paris, J. B. Baillière & fils, 1864.

3. Heidingsfeld, M. L.: The Pathology of Chromidrosis, J. A. M. A. **39**:1519 (Dec. 13) 1902.

REPORT OF CASE

Mrs. R. F., aged 48, complained of colored perspiration which stained her clothing. The sudden onset of the condition dated back five months. The patient had passed through the menopause three years previously without any abnormal consequences. On careful questioning as to her diet and living habits, nothing of significance was obtained. No other members of her family had any similar condition.

Physical examination revealed a rather obese white woman apparently in good health, with no abnormalities except chronic bronchitis. A cholecystogram revealed a normally functioning gallbladder. The results of studies of the blood, consisting of cell counts, determination of the icteric index, a van den Bergh test and chemical examination, were essentially normal. Urinalysis gave normal results. Perspiration was induced in the patient by placing her in a hot room and keeping her hands submerged in hot water. The perspiration that exuded from her entire body, including her scalp, was golden yellow, about the color of orange peel. Tears, caused by smelling aromatic spirits of ammonia, were also golden yellow. After surgical cleansing of the skin, cultures of the perspiration gave negative results.

Omitting various pigmented foods from the diet caused no alteration in the condition. Finally, after five weeks' observation, it was suggested that the patient discontinue using face powder. Within two days the condition had subsided, and since that time, about a year ago, there has been no recurrence.

After learning the cause of the condition, the patient burned the face powder which she had been using, thus making it impossible to obtain a sample for anlaysis.

This case illustrates the fact that localized absorption of a dye through the skin can give rise to a generalized excretion of the dye by the sweat glands of the entire body. In this case the dye was excreted even by the tear glands.

EFFECT OF ADDING CHLOROBUTANOL TO BISMUTH SUBSALICYLATE IN OIL INJECTED INTRAMUSCULARLY

HAROLD F. HOEFER, M.D., NEW YORK

This study was undertaken to ascertain whether the addition of chlorobutanol to a suspension of bismuth subsalicylate in oil would produce any untoward effect when the preparation was administered by intramuscular injection. A series totaling 1,440 injections was given to 137 adult patients in the syphilologic division of the clinic under the supervision of Dr. G. D. Astrachan.

Bismuth subsalicylate, 0.13 Gm., suspended in 1 cc. of olive oil with the addition of 3 per cent chlorobutanol was used, and as a control, bismuth subsalicylate, 0.13 Gm., suspended in 1 cc. of olive oil without chlorobutanol or any other addition.

Seven hundred and twenty injections were given of each preparation. Both preparations were given by the same members of the staff in the conventional manner, 2 cc. being injected into the upper outer quadrant of the buttock. Each patient received an intramuscular injection of each preparation alternately once

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.

weekly, and no patient knew which preparation was used at a particular time. On each visit careful inquiry was made as to pain following the injection. Three complaints were elicited, two after the injection of the bismuth in oil control and one after the injection of bismuth in oil with chlorobutanol. There was no instance of severe pain.

CONCLUSION

The preparations used were equally well tolerated, and there was no undesirable effect from either.

In my series the addition of chlorobutanol did not reduce or increase local reactions or symptoms attributable to the injection.

Obituaries

CHARLES AUGUSTUS SIMPSON, M.D.

1882-1939

Dr. Charles Augustus Simpson died suddenly of heart failure, at the age of 57, on Dec. 9, 1939. Gus, as he was affectionately called by his many friends and colleagues, was head of the department of dermatology and syphilology of the George Washington University School of Medicine. He was one of the pioneers in the treatment of cancer of the skin with radium and roentgen rays. He also contributed many scientific articles on dermatology. He was connected with the staffs of the Central Dispensary and Emergency Hospital, Episcopal Hospital, Gallinger Municipal Hospital and George Washington University Hospital, Washington, D. C., and had previously been on the staff of the New York Post-Graduate Medical School and Hospital, New York. Dr. Simpson attended many medical meetings, and his jovial presence will be missed in the future. His death removes a prominent figure in dermatologic circles of this country.

L. McC.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

A NECROPSY SURVEY OF CARDIOVASCULAR SYPHILIS WITH PARTICULAR REFERENCE TO ITS DECREASING INCIDENCE. J. W. WELTY, Am. J. M. Sc. **197**:782 (June) 1939.

After reviewing the records of 15,000 consecutive cases in which autopsy was performed in a period of ten years, Welty concludes that syphilitic cardiovascular disease as a cause of death has decreased at least 50 per cent. This decrease is sharper than that for tuberculosis. It is believed that the decreasing incidence may be explained by modern methods of therapy. Cardiovascular syphilis was found at 7 per cent of the autopsies. There were 192 instances of aortic aneurysm, 245 of regurgitation and 632 of simple aortitis. The expected prevalence in the Negro race was found, associated with more severe involvement. The author states that fatal cardiovascular syphilis before the fifth decade is an extreme rarity in the white race.

ON THE TREATMENT OF RAYNAUD'S DISEASE WITH PAPAVERINE INTRAVENOUSLY. M. G. MULINOS, ISRAEL SHULMAN and ISIDOR MUFSON, Am. J. M. Sc. **197**: 793 (June) 1939.

In the experience of the authors, treatment of Raynaud's disease with histamine iontophoresis applied to the hands and papaverine hydrochloride given intravenously led to (1) increase in the volume of the vascular bed and in the rate of blood inflow, (2) complete alleviation of the syncope, cyanosis and pain and (3) healing of trophic lesions.

HERPES ZOSTER AND ITS VISCERAL MANIFESTATIONS. ELMER S. GAIS and ROBERT H. ABRAHAMSON, Am. J. M. Sc. **197**:817 (June) 1939.

Gais and Abrahamson reviewed the records of 137 patients whose herpes zoster was severe enough to require hospitalization. Recurrence was noted in 8 cases. Adenopathy was pronounced in only 6. Bilateral zoster was observed only once, though there were 3 patients with concomitant varicelloid lesions, in 1 of whom encephalomyelitis developed. Various derangements of the central nervous system were found in 7 cases. There was an increase of the cell count in the spinal fluid in 5 of the 11 cases in which it was examined.

In 6 cases the appearance of a fiery red erythema led to a diagnosis of erysipelas on admission to the hospital.

The authors were particularly interested in 42 patients with symptoms referable to the viscera, 7 of these having pulmonary implications, 4 cardiac, 25 abdominal and 6 renal. Such symptoms are discussed with reference to errors in diagnosis and also to the possibility of organic involvement due to the virus's being transmitted centripetally along vegetative pathways.

LYNCH, St. Paul.

THE TREATMENT OF POSTARSPHENAMINE JAUNDICE. LOUIS J. SOFFER, Am. J. Syph., Gonor. & Ven. Dis. **23**:577 (Sept.) 1939.

In 1 per cent of patients undergoing antisyphilitic treatment jaundice develops, with a mortality rate of from 1 to 6 per cent. Soffer stressed the value of a high carbohydrate diet as a therapeutic measure. Such diets should consist of 400 to 600 Gm. of carbohydrates per day, divided into five or six feedings. In certain cases the diet should be supplemented with dextrose injected intravenously and insulin

given only when glycosuria is manifested. The use of cholagogues and choleretics in the treatment of jaundice due to arsphenamine is an unsound form of therapy.

THE MALARIAL TREATMENT OF GENERAL PARESIS: RELATION OF THE HEIGHT, DURATION AND FREQUENCY OF FEVER TO THE CLINICAL AND SEROLOGIC RESULTS. ISRAEL KOPP and HARRY SOLOMON, Am. J. Syph., Gonor. & Ven. Dis. **23**:585 (Sept.) 1939.

In a group of 182 patients with dementia paralytica to whom therapeutic fever (malaria) treatment was given and whose clinical status was known, the amount of fever with temperatures of 104, 105 or 106 F. and above did not make any significant statistical difference in the clinical results. The best clinical results were obtained when more than one hundred and fifty hours of fever above 100 F. was experienced. Patients who were subjected to more than ten malarial paroxysms showed the best clinical results.

A distinct relation is found to exist between serologic changes and time, regardless of the maximum temperature experienced, the percentage of serologic negativity increasing with each successive year.

SULFANILAMIDE IN CHANCROID DISEASE. ROBERT G. GREENBLATT and EVERETT S. SANDERSON, Am. J. Syph., Gonor. & Ven. Dis. **23**:605 (Sept.) 1939.

The judicious use of sulfanilamide in the treatment of chancroid was found efficacious and safe in the authors' hands. Sulfanilamide proved more efficient than any of the standard methods in vogue, succeeding where vaccine therapy frequently failed.

DEATH FOLLOWING MAPHARSEN THERAPY. S. D. SIMON and A. IGLAUER, Am. J. Syph., Gonor. & Ven. Dis. **23**:612 (Sept.) 1939.

This is the first fatality to be reported as a result of antisyphilitic therapy with mapharsen. Stomatitis, anuria and death followed five injections of the drug.

A SIMPLIFIED TECHNIC FOR ADMINISTERING OLD ARSPHENAMINE. A. BENSON CANNON, Am. J. Syph., Gonor. & Ven. Dis. **23**:621 (Sept.) 1939.

Because of his conviction that old arsphenamine is the drug of choice in the treatment of early syphilis, Cannon has devised a simplified technic for administering the drug. A 1 per cent solution (0.1 Gm. of arsphenamine in 10 cc. of fluid) of arsphenamine properly alkalinized is given by the syringe method. A 2 per cent solution was found to be easily tolerated by children. The solution is given by injecting 3 to 5 cc. at one time, pausing for twenty to thirty seconds and then injecting 3 to 5 cc. again, continuing with the injections and rest intervals alternately until all the fluid is injected. The usual individual dose of arsphenamine is 0.2 to 0.4 Gm. for men and 0.15 to 0.3 Gm. for women.

In clinical trials of this new method, in over 1,000 cases of syphilis in all stages there were no reactions which could be attributed either to the concentration of the solution or to the method of administration. The reactions encountered under the new method were not essentially different from those encountered under the old one except that a larger proportion of them were mild and immediate and the proportion of severe delayed reactions was correspondingly smaller.

REUTER, Milwaukee.

PERIARTERITIS NODOSA. ALFRED W. HARRIS, GEORGE W. LYNCH and JAMES P. O'HARA, Arch. Int. Med. **63**:1163 (June) 1939.

The authors add 6 examples to the 95 acceptable cases of periarteritis nodosa in the English literature. They analyzed the series for frequency of symptoms

and signs, the most constant changes being fever, leukocytosis and albuminuria. Purpura or cutaneous nodules were each found in about 20 per cent of the cases. Various other dermatoses appeared in individual cases.

HAVERHILL FEVER: REPORT OF A CASE WITH REVIEW OF THE LITERATURE. ELLISTON FARRELL, GEORGE H. LORDI and JOSEPH VOGEL, Arch. Int. Med. **64**:1 (July) 1939.

The authors present the clinical and bacteriologic findings in the fourteenth sporadic case of Haverhill fever to be reported. This disease, caused by infection with Haverhillia multiformis, is sometimes spoken of as "rat bite fever," a term which leads to confusion with sodoku, an infection with Spirillum minus. Both diseases may follow a rat bite, though such a history is not always obtained in the case of Haverhill fever.

Haverhill fever is accompanied by painful arthritis and is characterized by a continued remittent fever or by a periodic intermittent fever; the febrile reaction of sodoku is of the latter type. Arsenical therapy has no effect on Haverhill fever, while the effect on sodoku is specific.

Both diseases have cutaneous manifestations but must not be regarded as simple dermatologic conditions. The eruption of Haverhill fever may be confused with one of the erythemas (infectious erythema or erythema multiforme). In the case reported by the authors a maculopapular eruption was present on the extensor aspects of the legs. The eruption continued throughout the disease, leaving pigmented areas and later causing desquamation. Small petechiae were also noted and were present on the fingers as well as on the legs. The authors characterize the eruption of Haverhill fever as embolic, in contrast with the allergic nature of the eruption of sodoku.

LIMITATIONS OF BIOPSY OF STERNAL MARROW. E. V. KANDEL and G. V. LEROY, Arch. Int. Med. **64**:121 (July) 1939.

Kandel and LeRoy reviewed their experience with biopsy of sternal marrow and found that it was a superfluous link in the diagnostic chain more often than it was the sole means of establishing a diagnosis. When the biopsy was diagnostic of leukemia they found no instance in which the diagnosis was not established by other clinical means. As negative evidence the biopsy of sternal marrow is of somewhat greater usefulness. The authors emphasize that if considered without other clinical data the results of this procedure can be misleading.

METASTATIC CALCIFICATION: REPORT OF TWO CASES. DAVID M. GRAYZEL and MAX LEDERER, Arch. Int. Med. **64**:136 (July) 1939.

Grayzel and Lederer report 2 cases of metastatic calcification. In the first the condition was associated with a leukemic myelosis; in the second it complicated a normal pregnancy in an apparently healthy young woman.

The authors divide pathologic calcification into two types: the type in which the lime salts are deposited in previously diseased tissue and the type in which the salts are deposited in apparently healthy tissue. They regard as unnecessary the distinction between calcinosis universalis, with no increase of calcium in the blood, and metastatic calcification, in which there is hypercalcemia. They also regard the level of diffusible calcium as more important than the level of total calcium.

A CASE OF ARRHENOBLASTOMA WHICH SIMULATED CUSHING'S DISEASE. C. KELLY CANELO and HANS LISSER, Endocrinology **24**:838 (June) 1939.

Obesity, amenorrhea and hirsutism were noted in a patient having other characteristics of Cushing's syndrome. Because there was roentgenologic evidence of enlargement of the sella, the surgical removal of the pituitary gland was attempted,

but only fibrous tissue and atrophic pituitary cells were found. The growth of hair on the face decreased greatly in the following six months. The patient subsequently died of a tumor of the ovaries.

In speculating as to the reason for the improvement of the hypertrichosis, Canelo and Lisser state that a pituitary cyst may have been ruptured at the time of the operation. This case illustrates the difficulties in arriving at a differential diagnosis of arrhenoblastoma, adrenal cortical syndrome and Cushing's disease.

INFLUENCE OF ULTRAVIOLET IRRADIATION UPON EXCRETION OF SEX HORMONES IN THE MALE. ABRAHAM MYERSON and RUDOLPH NEUSTADT, Endocrinology **25**:7 (July) 1939.

Myerson and Neustadt found that ultraviolet irradiation increases the excretion of androsterone in urine and that irradiation of the scrotum and its vicinity proves to be more effective than irradiation of other parts of the skin. Casual and incomplete observations concerning estrogens suggest that the rise in their excretion is slower, lower and more retarded than that of androgens.

URINARY EXCRETION OF ESTROGENIC SUBSTANCES AFTER ADMINISTRATION OF TESTOSTERONE PROPIONATE. RALPH I. DORFMAN and JAMES B. HAMILTON, Endocrinology **25**:33 (July) 1939.

In immature monkeys the results of intramuscular injections of large amounts of testosterone propionate are suggestive of increased excretion of estrogen, indicating that some portion of the output of estrogen by normal men may be a result of the influence of androgen.

PROTECTIVE ANTIBODIES IN THE SERUM OF SYPHILITIC RABBITS. THOMAS B. TURNER, J. Exper. Med. **69**:867 (June) 1939.

Turner reports a series of experimental studies which indicate that specific humoral antibodies are produced during the course of syphilitic infection in rabbits. These protective antibodies were found in the serum of rabbits resistant to reinfection.

LYNCH, St. Paul.

A LIST OF SUBSTANCES FOR PATCH-TESTING AND THE CONCENTRATIONS TO BE EMPLOYED. ADOLPH ROSTENBERG JR. and MARION B. SULZBERGER, J. Invest. Dermat. **2**:93 (June) 1939.

A long and useful list of substances is given, with the concentration in which they may best be employed for patch tests. The list is tabulated so as to show the vehicle for the substance and the concentration to employ, and the substances are classified according to the occupation or trade in which they are encountered.

ON THE SKIN TEST IN LYMPHOGRANULOMA INGUINALE [VENEREAL LYMPHOGRANULOMA]. II. WILHELM FREI, J. Invest. Dermat. **2**:119 (June) 1939.

Frei states that the most common errors in the use of the cutaneous test (Frei test) for venereal lymphogranuloma result from nonspecific reactions produced by the contamination of the vaccine with living or dead bacteria. A vial with a rubber stopper having a depressed center was used to hold the vaccine instead of the previously used vial with a rubber cap. The stoppered vial with iodine as the disinfectant was tested bacteriologically and, although not completely free from contamination, was found to be superior to the capped vial with 80 per cent alcohol as the disinfectant. Because even with the strictest technic and permanent refrigeration the improved method was not entirely free from contamination, Frei prefers ampules as containers for the vaccine. He describes his own method of preparing the vaccine and performing the test. Warning is given against making

the test on patients with acute conditions (high fever or severe inflammation) until the symptoms subside. He advises that the test be avoided entirely for patients with venereal lymphogranuloma with buboes, rectal stricture or severe inflammatory or suppurative processes near the peritoneum. In the cases of anergic venereal lymphogranuloma with buboes (not the early conditions, in which before allergy is fully developed the reactions may still be negative) in which the result of a cutaneous test is persistently negative, the inverted test is suggested. In this test sterilized pus from a patient's bubo is injected into the skin of persons with proved venereal lymphogranuloma producing a positive local reaction.

PRODUCTION OF POSITIVE SEROLOGIC REACTIONS IN RABBITS AND THE SUBSEQUENT REACTIONS OF THE SEROLOGICALLY-ALTERED ANIMALS TO INOCULATION WITH SPIROCHETA PALLIDA. FREDERIC T. BECKER, J. Invest. Dermat. **2**:125 (June) 1939.

Rytz's work of producing positive Wassermann and flocculation reactions in rabbits' blood by the injection of flocculate obtained from the serum of patients with syphilis (untreated latent and tertiary syphilis) was repeated. The flocculate consisted of syphilitic blood serum plus cholesterolized alcoholic extract of beef heart. Animals treated in this manner and then innoculated with Spirochaeta pallida were found to have a longer incubation period previous to showing clinical evidence of infection than did the control animals. This fact was taken to be a manifestation of altered susceptibility to syphilitic infection. The human syphilitic flocculate was thought to be definitely antigenic, because ten times the original quantity injected into the rabbit was later obtained from the same rabbit.

CLINICAL AND EXPERIMENTAL STUDY OF INTERSTITIAL KERATOSIS. JOSEPH V. KLAUDER, ELMER R. GROSS and HAROLD F. ROBERTSON, J. Invest. Dermat. **2**: 157 (Aug.) 1939.

Theories and experiments relative to the cause of syphilitic interstitial keratitis are discussed. It may be caused by (*a*) a direct invasion by Spirochaeta pallida, (*b*) an allergic reaction or (*c*) a nutritional disturbance. Some of the pertinent experiments have been repeated by the authors. S. pallida could not be demonstrated in pieces of cornea removed from 4 patients with interstitial keratitis. There was no evidence of allergic reaction in the cornea of rabbits injected intraocularly with horse serum. Cutaneous tests with the patients' own cornea and with the cornea of a syphilitic fetus in patients with interstitial keratitis also gave negative results. Interstitial keratitis could not be produced in syphilitic rabbits by repeated trauma of the cornea.

Studies were also made on the treatment of interstitial keratitis with the application of heat, by means of the thermophore (an instrument used to heat the cornea), both experimentally on rabbits and clinically in the treatment of patients. It was observed that the temperature required to kill S. pallida was at least 120 F. for two minutes, while the maximum temperature the cornea could tolerate with safety was 130 F. for one minute. Thermophore treatment of the involved eye could not be said to influence favorably the course of the disease, nor did treatment of the uninvolved eye prevent the subsequent occurrence with interstitial keratitis.

The absorption of neoarsphenamine by the cornea, after instillation into the conjunctival sac, and the penetration of the drug into the cornea, after its intravenous administration in rabbits, were studied. No arsenic was present in the cornea after successive instillations of a 1:600 dilution of neoarsphenamine. But after six daily intravenous injections of 30 mg. per kilogram of body weight of neoarsphenamine, 0.04 mg. of arsenic was found in each cornea. The involved and uninvolved eyes of patients with interstitial keratitis were treated by the instillation of neoarsphenamine, but the course of the disease was not influenced.

DAVIS, Nashville, Tenn.

LUPUS ERYTHEMATOSUS OF THE CONJUNCTIVA. F. I. YOUSEFOVA and S. N. BOGDANOVITCH, Ann. d'ocul. **176**:27 (Jan.) 1939.

Lupus erythematosus of the conjunctiva is rare. In the literature accessible to the authors, only one article could be found which related to the subject.

This report concerns an adult of 23 years who came to consultation in 1935 for a bilateral ocular condition. The malady had followed an injury to the right eye three years previously, after prolonged working in the field in the sun. The palpable swelling of the right eye was followed by an eruption of spots on the cheek and lids accompanied by photophobia and tearing. The following year the left eye became similarly affected. Since that time the patient had been treated with drops and ointments without relief. On the contrary, the spots as well as the photophobia, tearing and ocular pain increased.

Considerable further detail of the general examination is given, with three photographs. The extraordinary rarity of lupus erythematosus of the conjunctiva is to be explained in part by the fact that the symptoms are not severe enough to complain of or to be brought to the attention of the ophthalmologist or the dermatologist.

McKEE, Montreal, Canada. [ARCH. OPHTH.]

MULTIPLE CUTANEOUS ABSCESSES WITH RECURRENCE IN A NURSLING. A. BERAUD, Arch. de méd. d. enf. **41**:736 (Nov.) 1938.

A girl 1 year of age suffered from multiple abscesses of the scalp. The parents had both sustained attacks of furunculosis, and the mother's blood, fortified by specific and polyvalent vaccines, was used for immunotransfusion. This method of treatment had been successfully used by the author in many previous cases, including that of a sister of the patient, but in the present instance it resulted in complete failure. After a short period of relief, a succession of abscesses appeared over the neck and body. At this point the treatment was changed and anti-staphylococcus anatoxin substituted for the hemotherapy. The amount injected was gradually increased from 0.2 to 0.7 cc. Recovery was rapid and permanent.

CALCIFIED AND MUMMIFIED EPITHELIOMAS OF THE SKIN IN CHILDREN. M. FÈVRE, R. HUEGUININ and F. VELIZ PAIZ, Arch. de méd. d. enf. **42**:73 (Feb.) 1939.

Epitheliomas of this type are benign in their evolution but have many unsolved features in their pathogenesis. After operating in 7 cases, the authors made an exhaustive study of tumors of the skin in young subjects. They believe these growths to be much more common than is generally considered, especially in early life; one report concerns an infant of 3 months, and six reports in the literature concern nurslings varying in age up to 6 months. The development of the epithelioma is insidious; the evolution is extremely slow and entirely free from pain; the tumor is slightly more frequent in females. The discovery of the tumor is usually accidental. The essential characteristics are great induration, adherence to the skin and total absence of involvement of the deeper tissues. The site of the tumor is practically always either the face or the neck, but cases have been reported in which the growth involved the arm or the leg. Ulceration of the skin may occur, with discharge of calcareous material. Recurrent tumors have been observed, but multiple growths are rare. A full discussion of the histologic observations, chemical characteristics and treatment follows.

A MALIGNANT TYPE OF ACRODYNIA. L. CAUSSADE, J. WATRIN and N. NEIMANN, Arch. de méd. d. enf. **42**:91 (Feb.) 1939.

Up to this time, the aspect of malignancy has never been considered in the study of acrodynia. The investigations of Marquezy and Ladet have called attention to a particularly severe type of this disease in the eastern part of France. Four

cases are reported in children varying in age from 16 months to 6 years; all were similarly affected. After several weeks the benign invasion suddenly assumed alarming features, the brunt of the attack being borne by the nervous system in the form of asthenia, adynamia and unconsciousness, with corresponding changes in expression and great disturbances in the circulatory and respiratory systems. Later the digestive apparatus was attacked, but no visceral symptoms were noted in any case. Three deaths occurred in this series, and autopsy disclosed striking changes in the tissues of the brain and the sympathetic nervous system.

LIPODYSTROPHY AND LIPOMATOSIS FROM REPEATED INJECTIONS OF INSULIN. P. NOBÉCOURT and P. DUCAS, Arch. de méd. d. enf. **42**:193 (April) 1939.

A girl of 16 years in whom diabetes had developed at the age of 9 and who had received several injections of insulin daily either in the thigh or in the hip for a period of six years had at these sites, at the time of examination, small tumors with all the physical aspects of lipomas. The tumors varied in size from that of a small nut to that of an orange and were painless and elastic. The skin was streaked and bluish.

With the introduction of protamine zinc insulin, one injection daily in the arm, the tumors of the thighs rapidly disappeared, but those on the hips regressed slowly and could readily be seen a year later. Estimations of the blood cholesterol showed it to be within normal limits.

A girl of 14 who had suffered from diabetes for six years and for several years had had daily injections of insulin in the thigh presented atrophic areas as large as the palm of the hand and about 2 cm. in depth. The skin was normal in appearance but could not be picked up easily and seemed to be deprived of all subcutaneous fat. These atrophic areas remained unchanged after a year, although protamine zinc insulin was substituted and different sites of injection insisted on.

A third observation, similar to the one just described, is reported concerning a girl of 18 who had been diabetic since the age of 10.

A review of the now abundant literature on this condition, the pathologic nature of which is not understood, terminates the contribution.

AMESSE, Denver. [AM. J. DIS. CHILD.]

PHAGEDENIC ECTHYMA IN AN INFANT. G. CARDELLE, B. SANTIAGO and A. G. LOPEZ, Arch. de med. inf. **7**:380 (July) 1938.

The authors present a case of phagedenic ecthyma in a boy aged 1 year. There was an ulcer on the hypogastrium, extending to the left lumbar region, and there were other smaller ones on the back and extremities.

Cultures showed the hemolytic streptococcus.

The spread was rapid but without much necrosis, and the general symptoms were pronounced.

Local applications of an antiseptic paste and gentian violet were used in the course of treatment. Blood transfusions were also given.

SCHLUTZ, Chicago. [AM. J. DIS. CHILD.]

Society Transactions

AMERICAN DERMATOLOGICAL ASSOCIATION, Inc.

FRANCIS E. SENEAR, M.D., *President*

FRED D. WEIDMAN, M.D., *Secretary*

Clinical Meeting, Monte-Bello, Quebec, Canada, May 31, 1939

Lingua Nigra. Presented by DR. J. F. BURGESS, Montreal, Canada.

F. M., a white woman aged 33, was first seen May 2, 1939, on account of a marked black "hairy tongue," first noticed by her in February. She was given

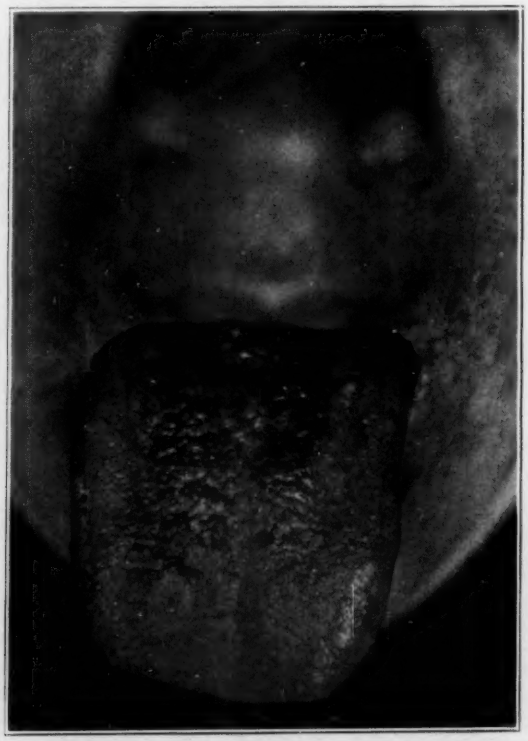

Fig. 1 (F. M.).—Lingua nigra.

daily doses of 100 mg. of nicotinic acid by mouth, beginning on May 12. There was gradual improvement, so that at the time of her presentation, after six weeks' therapy, little trace of the condition remains.

DISCUSSION

DR. ARTHUR M. GREENWOOD, Boston: At the Huntington Clinic in Boston, many cases of carcinoma of the tongue are observed, and black hairy tongues

frequently follow irradiation in these cases. The papillae become hypertrophic and secondarily infected. It may be that the patients have a deficient diet, because of the difficulty in eating.

Syphilis with Negative Serologic Changes: Exfoliative Dermatitis. Presented by DR. DONALD S. MITCHELL, Montreal, Canada (by invitation).

B. B., a woman aged 20, presented an early secondary syphilitic eruption, with a positive Wassermann reaction, on Jan. 26, 1939. After the third injection of neoarsphenamine, eight days after the beginning of treatment, an erythema developed. Two days after the fourth injection a generalized erythema multiforme eruption developed. This spread and became a generalized erythroderma, with temperature to 100 F. Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was given, and the eruption quieted. After one week, her temperature went to 104 F., with aggravation of all signs and symptoms. There were pains in the joints, headache and increase in scaliness.

A vulvar discharge, present on admission, showed no organisms, but the complement fixation test for gonococci gave strongly positive results.

Sulfanilamide was administered, with gradual subsidence of the condition.

On February 20 the Wassermann reaction was strongly positive, and on March 1 the colloidal gold reaction of the spinal fluid was 0011100000. On March 22 the Wassermann and Kahn reactions were negative, and the complement fixation test for gonococci gave a negative result. Ten days later the reactions of the spinal fluid were normal.

NOTE.—Wassermann tests made in June and August were negative. Treatment with a bismuth preparation is being continued.

DISCUSSION

DR. LOREN W. SHAFFER, Detroit: The reversal of the serologic reactions could be accounted for on the basis of the treatment received plus the fever that developed, a protracted fever with the temperature as high as 104 F. The history of the administration of sulfanilamide brings up several problems, of which the first is the attack of erythema multiforme that the patient evidently had. The beneficial results from the use of sulfanilamide in the treatment of this condition would be explainable if there were the possibility of gonorrhea. The fever, however, that developed in this patient seven days after the use of sulfapyridine was interesting. I have been interested in this type of reaction to sulfanilamide and have an impression that in some cases it may be explainable on the basis of a ninth day erythema. One sees various types of toxic reactions following the use of sulfanilamide after a week to ten days. They are often associated with various toxic eruptions similar to those that occur after the use of arsphenamine in the treatment of syphilis. Further, arsphenamine therapy may be used after such a reaction. In this case, sulfanilamide was used after the reaction, and the fever subsided. I believe that the toxic reactions are not necessarily contraindications to the further use of sulfanilamide.

DR. DUDLEY C. SMITH, Charlottesville, Va.: It should be mentioned that sulfanilamide itself is an agent that will cause fever. I have encountered 2 cases in which its administration was responsible for the fever. It is not known by what mechanism the reaction is produced.

It is my impression that the concomitant administration of sulfanilamide and arsphenamine increases the incidence of untoward cutaneous reactions.

DR. DONALD S. MITCHELL, Montreal, Canada (by invitation): The patient had little in the way of treatment, only four injections of arsphenamine and four injections of a bismuth preparation. Four or five months after the initial eruption the serologic reaction is still negative. Probably the patient will be given routine treatment except for the arsenicals.

Extensive Keloid Following Lightning. Presented by DR. J. F. BURGESS, Montreal, Canada.

R. M., a white boy aged 17, came to the clinic eight years ago on account of extensive nodular linear keloids on the forehead, chin and arms. He had been struck with lightning about six months previously while riding his bicycle. The burns from lightning had caused severe cicatricial contractures involving the joints of the elbow and wrist. Special surgical measures were attempted, but owing to the vascularity of the tissue the resulting hemorrhage was controlled with great difficulty. After this, roentgen therapy was instituted, followed by considerable flattening of the lesions.

The patient was presented before the Atlantic Dermatological Conference in Montreal in 1932.

Tertiary Syphilis. Presented by DR. J. F. BURGESS, Montreal, Canada.

N. F., a Greek aged 71, presents on the right leg and ankle an eruption of areas of linear and irregularly shaped atrophic scars, with pronounced peripheral pigmentation. Several rather brownish infiltrated lesions at the periphery apparently represent the primary lesion. The eruption has been present two years.

The general condition is good except for moderate secondary anemia. The Wassermann reaction of the blood is strongly positive.

The histologic picture revealed a cicatricial process in the upper layers of the corium, with thinning of the epidermis. Small foci of lymphocytes were scattered through this area, in some of which an occasional multinucleated giant cell was present. In some places there was also a slight perivascular grouping of this infiltration.

DISCUSSION

DR. J. F. BURGESS, Montreal, Canada: The only reason this case is presented is because of the areas of linear scarring which look like typical gouged-out lesions recurring in some places. I suppose that one might consider that neurotic excoriations have occurred over an underlying syphilitic manifestation.

DR. HOWARD FOX, New York: As I remember, this man had a unilateral eruption, with grouped scars on one leg and a lesion surrounded by hyperpigmentation. I think the clinical signs alone are strongly in favor of a late syphilid. Incidentally, the Wassermann and Kahn reactions of the blood were positive.

Lupus Vulgaris Disseminatus. Presented by DR. DONALD S. MITCHELL, Montreal, Canada (by invitation).

Mrs. P., an otherwise healthy-appearing woman aged 33, in whom tuberculous cervical adenitis, scrofuloderma and lupus vulgaris developed twenty-five years

ago, following measles, presents well demarcated brownish infiltrated patches on the skin of the face, neck, shoulders and arms. Reactions to tuberculin were positive, with no evidence of tuberculosis elsewhere. Histologic examination showed a typical tuberculous structure. Treatment in the hospital and outpatient department has consisted of ultraviolet irradiation (local and general), a high vitamin and low salt diet, intravenous injections of gold sodium thiosulfate and neoarsphenamine, local injections of phenylethyl hydnocarpate and excision.

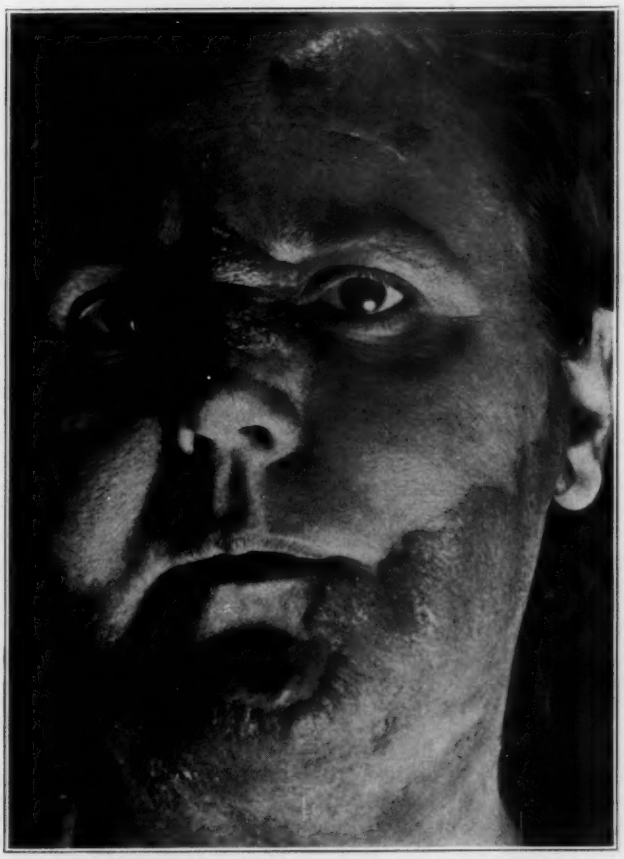

Fig. 2 (Mrs. P.).—Lupus vulgaris disseminatus.

DISCUSSION

DR. MARION B. SULZBERGER, New York: I should like to suggest that the diagnosis be changed in so far as the word "disseminatus" is concerned. Lupus vulgaris disseminatus is usually a different type of eruption: an exanthematous form of lupus vulgaris in which many areas of the body are affected, including the extremities. I think that the condition in this case might best be called lupus vulgaris tumidus.

Recurrent Vesicopustular Eruption on the Extremities. Presented by Dr. J. F. Burgess, Montreal, Canada.

J. P., a white woman aged 30, presents a vesicopustular eruption involving the palms and soles. The nails of the fingers and toes are dystrophic, with some friability of the distal parts. There is a tendency to some grouping of the eruption, especially over the heels. The total duration of the condition is one year. The general health is good, but there is a chronic infection of the tonsils. A search for fungi gave negative results.

Histologic examination showed a hyperkeratotic area of skin with several intraepidermal vesicles and microabscesses. The hyperkeratosis was flaky. The epidermis showed acanthosis and spongiosis, with fusion, some clubbing of pegs, occasional parakeratosis and a diminished granular layer. The vesicles contained a few polymorphonuclear leukocytes and lymphocytes. There was a perivascular and slight subepidermal infiltration of round cells and a few polymorphonuclear leukocytes. No eosinophils were seen.

Treatment consisted of fungicidal applications of varying kinds, soothing applications, injections of arsenic and roentgen therapy. Partial improvement resulted. In April 1939 her tonsils were removed, after which there was an immediate exacerbation of the eruption. Since then there has been little change.

Recurrent Vesicopustular Eruption on the Extremities. Presented by Dr. J. F. Burgess, Montreal, Canada.

A. L., a white woman aged 42, presents a grouped vesicopustular eruption on the left instep of about one year's duration.

Pertinent investigation has revealed a chronic ethmoiditis and frontal sinusitis on the right side. She had an inflammatory condition in the pelvis two years ago. Microscopic investigation on two occasions failed to reveal fungi, and cultures were negative.

Histologic examination showed a flattened epidermis, with infiltration by polymorphonuclear leukocytes. The scale was hyperkeratotic in part, with retention of nuclei and staining properties of the rete. The corium showed some infiltration of round cells and scarring.

DISCUSSION ON CASES OF VESICULOPUSTULAR ERUPTION

Dr. George C. Andrews, New York: I was particularly interested in these 2 cases, and I should consider the conditions in both to be a bacterid. The histologic picture in both, however, is different from that in the cases that I have observed. The lesions in the 2 cases are superficial. In the latter case, that of A. L., the vesicle is impetiginous and near the surface. The histologic structure is different in the 2 cases. In A. L. there is a notable lymphocytic infiltration underlying the impetiginous vesicular areas. In J. P. there is practically no inflammatory reaction at all beneath the superficial vesicles.

The first of the 2 patients presented says that she is much better now than she was last summer, when she could not stand or walk at all and the vesicles or pustules were large and painful. Since then she has been on a Sippy diet, which has cured her peptic ulcer. That may be significant. The fact that a flare-up occurred after removal of the tonsils two months ago is also interesting. Not sufficient time has elapsed to judge the effect of removal of the tonsils. If it has not already been done, I suggest an examination of the cervix, because it is possible that there might be a further focus there. I should like to know what the blood count is.

For the second patient I suggest treatment of the ethmoiditis and frontal sinusitis. It is difficult to see the tonsils without a tonsil hook, as the anterior pillar almost hides them, but there is evidence of an inflammatory reaction in the throat. Mycologic examination must also be made. I do not see any clinical or histologic signs of psoriasis in either of the patients.

DR. HAROLD N. COLE, Cleveland: The onychomycosis in J. P. is significant. Until the onychomycosis is taken care of, one cannot expect further clinical progress.

DR. SAMUEL AYRES JR., Los Angeles: I think that the changes in the nails of J. P., unless microscopic examination proves otherwise, are psoriatic. There are rather typical stippling, thickening and piling up underneath. I should like to ask if cultures have been made for fungi. I think that in view of the changes in the nails the diagnosis of psoriasis ought to be considered.

DR. J. F. BURGESS, Montreal, Canada: My first impression was that the condition in J. P. was a frankly pustular psoriasis, but, on the other hand, I was undecided about A. L. I felt that it was difficult indeed to make a diagnosis of pustular psoriasis on the appearance of the face alone, unless there was a coincident typical psoriasis of the body. I say that because I have seen a patient at intervals for the past twelve years on account of a recurring and persistent pustular eruption on the heels, which always suggested a fungous or coccic infection, although I could not demonstrate a fungus. In the last year a widespread clinically typical psoriasis has developed. I therefore, with a good deal of hesitancy, made a diagnosis between a pustular bacterid of the Andrews type and pustular psoriasis.

Replying to Dr. Ayres' question, mycologic cultures were made, but there was no growth.

Kraurosis Vulvae with Leukoplakia. Presented by DR. BARNEY USHER, Montreal, Canada (by invitation).

Mrs. J. C., aged 51, had been under observation since 1924 for a severe and intractable pruritus of the genitalia. In 1934 the diagnosis of kraurosis vulvae with lichenification was made. Investigation revealed nothing of significance. Treatment with estrone (theelin) was of no value.

In September 1934 resection of the pudendal and perineal nerves was performed by Dr. A. D. Campbell. Since the operation the pruritus has completely disappeared except for an area about the clitoris, where it is considerably diminished. In that region there is persistence of mild leukoplakia. The leukoplakia elsewhere has disappeared. There has been no progression of the kraurosis since 1934. Senile vaginitis with leukorrhea has persisted in spite of various applications, including estradiol benzoate (progynon B) in full dosage. Histologic examination showed the epidermis to be thin and the papillae few and flattened, with small rete pegs. The keratin layer showed considerable thickening but in places was absent. The papillary layer was increased, while the fibrillary structure was largely lost. The tissue had a more or less homogeneous appearance, with scattered spindle-shaped nuclei and numerous capillary vessels. Scattered throughout this zone were lymphocytes, plasma cells and eosinophils. The infiltrating cells extended into deeper layers of corium, where there was also hyperplasia of the vessels with thickening of their walls.

Neurodermatitis. Presented by DR. BARNEY USHER, Montreal, Canada (by invitation).

Mrs. A. K., aged 50, was observed in 1935 with a silver dollar–sized plaque of neurodermatitis involving the upper and outer aspects of the left labium majus. This had been present for two years prior to observation. Chemical examination of the blood gave negative results.

Histologic examination showed great hypertrophy of the epidermis, with elongation of the rete pegs. The zona granulosa was practically absent, and there was superficial parakeratosis throughout the papillary zone. Scattered throughout the epidermis there was infiltration of lymphocytes and polymorphonuclear leuko-

cytes. There was a general hyperemia of the papillary zone and some slight edema. There was also in the papillary zone some pigmented chromatophores, although there was no excessive pigment in the basal layer.

Resection of the perineal and pudendal nerves was performed by Dr. A. D. Campbell in June 1936, and the patient has remained well.

Leukoplakia Vulvae. Presented by Dr. Barney Usher, Montreal, Canada (by invitation).

Mrs. M., aged 60, suffered for ten years from leukoplakia surrounding the clitoris, associated with severe pruritus. Investigation revealed a normal pelvis and a normal amount of blood sugar. Histologic examination showed decided hyperkeratinization and hyperplasia of the squamous cells. Prolongation of the interpapillary epithelium was marked. In some areas of the hyperplastic squamous epithelium there were accumulations of round cells. Some of these were hyperchromatic, while others were vesicular. They varied little in size and shape. Below the epithelium there were collections of similar cells in a hyalinized fibrous stroma. In places the stroma extended into the epithelium as finger-like projections. The cells in these did not differ remarkably from those apparently cut off in areas of the epithelium. The vessels were dilated and thin walled.

Resection of the sensory nerves of the perineum (Dr. G. J. Strean) in January 1938 was performed, with almost complete subsidence of the pruritus. Great improvement in the leukoplakia, at times complete disappearance, was observed.

DISCUSSION ON CASES OF LESIONS OF THE VULVA

Dr. Louis A. Brunsting, Rochester, Minn.: I think the condition in the case of Mrs. J. C. is an example of true kraurosis vulvae, with perhaps a suspicion of telangectasia and atrophy with actinodermatitis. I was interested in examining the patient's tongue to find that it shows marginal atrophy. Instances have been reported of generalized smoothing of the mucous membranes of the mouth and vulva. In the gynecologic literature some patients with this condition are reported to have improved under the administration of hydrochloric acid and cod liver oil. I suggest in this case that surgical excision of the vulva be considered if there is extension of the condition.

Dr. Harold N. Cole, Cleveland: I have recently had the opportunity of following several cases of kraurosis vulvae, in 1 of which the condition was extensive. The patients were given intramuscular injections of estrone (theelin) once a week (2,000 to 5,000 units), and the results have been remarkable. I have observed results from resection or excision of the areas of kraurosis, and it is my impression that one can get fully as good results from estrone (theelin) alone.

Dr. Henry D. Niles, New York: According to the description, the lesion is on the left labium majus. All I was able to find was an apparently atrophic patch on the right thigh and nothing on the labium majus.

Dr. Barney Usher, Montreal, Canada (by invitation): Any scar is the result of the removal of biopsy specimens. Both Mrs. J. C. and Mrs. A. K. received injections of estrogenic substance, one estrone (theelin) and one estradiol benzoate progynon B, but with no results. An interesting feature in the case of Mrs. M. is that a year ago she had a ½ inch (1.3 cm.) thickened area of leukoplakia. She now has almost complete relief from symptoms, with almost complete subsidence of the leukoplakia. The same holds true for Mrs. J. C., who obtained almost complete relief from pruritus, certainly more than enough to warrant further interference. The operation was done under spinal anesthesia, with no effect on the patient. Relief was almost immediate. One patient was followed for four years, another for five years. All symptoms have disappeared, and the patients have remained fairly well.

Atopic Dermatitis. Presented by DR. J. F. BURGESS, Montreal, Canada.

V. St. P., a white woman aged 37, shows a thickened, lichenified exudative and inflammatory eruption on the face, neck, upper part of the chest and back, cubital fossae and posterior aspects of the thighs. There are numerous excoriations. The eruption has been present for ten years, with some remissions during the first year of her illness. The general health has been good. There are no abnormal metabolic observations, and roentgenographic and special examination of the nose, throat, teeth, gallbladder and generative organs gave negative results.

Extensive cutaneous tests for protein showed a decided reaction to silk and dog hair (there had been a dog in her house for ten years). A decided reaction to silk material was obtained by applying it with moisture at the site of a linear scratch. A piece of the same silk applied to the unbroken skin under an occlusive dressing failed to cause a reaction in twenty-four hours.

Contact with silk has been removed, without any change in her eruption. Contact with dogs has not been entirely eliminated. A high vitamin diet and ample doses of capsules containing vitamins A, B, C, D and G have caused considerable improvement but have not resulted in cure.

DISCUSSION

DR. WILLIAM H. GOECKERMAN, Los Angeles: In my experience with atopic eczema and neurodermatitis, I cannot recall any instance in which treatment with the conventional methods has ever given satisfactory permanent results. I should like to bring up a point which I emphasized three years ago at the meeting of this association, when I received further encouragement in my point of view from the discussion by others. I think that in a definite subgroup of patients with this syndrome the disease is the result of a deficient diet. I cannot select these patients by objective appearance but have to be guided by the history. The condition does not occur necessarily among poverty-stricken people. This type of patient usually comes from a family in which the father is active and at home little and the mother leads the life of a club woman who leaves the care of the children to servants. There is an abundance of good food, and the meals which are provided are usually well balanced, but the child, often precocious, does not eat what is put on the table. I now have 3 cases in which this peculiar cutaneous picture, which I am beginning to look on as an entity, is present. With an adequate diet the response was striking and seemingly permanent. The exact element in which the food is deficient in these cases I do not know. For the present I can only suggest that a fully adequate diet be given when such a condition is suspected. One patient under my observation has gone for four years without a recurrence. At the time I started to give her this treatment she was 17 years old. I do not have enough cases of this type for study to evaluate this particular feature of the subgroup, and therefore I should like to call emphatic attention to it so that dermatologists who have a larger amount of material at their command will give it a trial. The best that I can suggest today is that dermatologists go into the history of their patients most carefully in order to ferret out a deficiency in the diet.

DR. MARION B. SULZBERGER, New York: I agree with Dr. Goeckerman concerning the difficulty of proving what role allergens play in the production of the clinical manifestations of the atopic cutaneous disease. It is particularly difficult to prove whether or not the removal of allergens benefits the patients and, if so, what percentage of them is benefited. I think that in some of these cases, particularly when more youthful persons are affected, allergens without question play a definite role. I also think that removal of specific factors from the food or environment of an adult rarely effects a cure or even gives great relief. The situation is much like that with asthma. In at least 50 per cent of the persons with asthma removal of allergens does not effect relief. However, the role of allergens in this case is easily seen. The patient gave reactions when the skin was tested not only with com-

mercial silk allergen but also with material from one of her own silk dresses. Moreover, the wearing of certain of her silk dresses has produced clinical exacerbations. In addition, a piece of silk dress moistened with potassium hydroxide and applied to normal skin without scratching led to the appearance of a large wheal and flare. I think that there is a definite demonstration that there can be transepidermal penetration of silk allergen and that the wearing of silk is under certain conditions inclined to produce wheals, itching and a tendency to scratch in this woman. It is, of course, obvious that this is not the whole story, even in this case, and that not only silk but many other things cause this patient to itch and scratch.

DR. J. HARPER BLAISDELL, Boston: I should like to point out some difficulties in removing offending allergens in such cases. The patient was wearing silk stockings. I do not think it is sufficient to tell a woman not to wear a silk dress if at home she exposes herself to a silk dress worn by her sister. This patient is sensitive to dogs and has been in contact with a dog for many years. I have always found it difficult to cleanse a home from the dander and hair of a dog. Removal of the dog is not sufficient; a thorough cleansing of the premises is also necessary. One must take into account not only the exposure of the patient to substances which he wears but also his contact with what other members of the family wear.

DR. GEORGE C. ANDREWS, New York: I should like to suggest that this patient try two or three things. One is that she use a nasal filter. These in a measure protect against pollens and other inhalants. Some of her trouble may be from inhalants as well as from substances with which her skin comes in contact. I have used nasal filters with some success in cases of allergic eczema due to inhalants. I also suggest passive transfer tests. One should test for reactions to several food materials, to silk and to dog hair. She might also be desensitized, by injections, if she can be, to substances to which she reacts positively. These measures probably will not cure her but should make her trouble less annoying.

DR. J. F. BURGESS, Montreal, Canada: In the past year and a half I have had a number of patients with atopic eczema who have improved under treatment with large doses of mixed vitamins. One of these, a young girl, had a persistent lichenified eczema of the face and neck, and a good many tests were done on her prior to the time I saw her. They showed that she was sensitive to a number of different allergens. I had the impression that she was getting little vitamin C in her diet, and so for one year I have given her large doses of ascorbic acid by mouth. Since that time not only has her eruption entirely disappeared, but also her attacks of nervous irritation. I think she belongs in the group of patients whom Dr. Goeckerman referred to.

DR. JOHN ANTHONY GAMMEL, Cleveland: One cause of the difficulties physicians encounter in approaching cases of atopic eczema by way of allergens is the great number of possibilities to be considered. There are cutaneous tests for a few hundred allergens but there are many more possibilities which one cannot detect unless one spends days with the patient. Suppose one finds out that he is sensitive to silk and to certain feathers. At the same time he may be allergic to a dozen unsuspected and unusual substances for which it is impractical to test. The known factors are eliminated, but the eczema persists because the other, unidentified causes have not been removed.

Danlos' Syndrome. Presented by Dr. BARNEY USHER, Montreal, Canada (by invitation).

E. C., a girl aged 7 years, presents hyperelasticity of the skin, hyperlaxity of the joints and a doughy feel of the skin. Scarred atrophic areas are present on the elbows, knees and forehead, associated with hemorrhage following slight injury.

The condition has been present since birth. The only pathologic change revealed by laboratory examination was increased fragility of the red blood cells.

Histologic examination showed changes in the fibers of elastic tissue. There were reduplication, fragmentation and condensation of the fibers, with a moderate degree of alteration of the collagen bundles.

DISCUSSION

DR. RICHARD S. WEISS, St. Louis: Dr. Usher was fortunate in getting an example of this peculiar syndrome: hyperelasticity of the skin, hyperlaxity of the joints and pseudotumors. The condition is not as marked as some I have observed in St. Louis. In some cases the hyperelasticity of the skin is so prominent that the skin can be pulled out 6 or 8 inches (15 to 20 cm.). The microscopic changes were consistent with those I have observed.

Case for Diagnosis (Phenolphthalein Pigmentation?). Presented by DR. DONALD S. MITCHELL, Montreal, Canada (by invitation).

S. S., a healthy boy aged 15 months, is presented with a generalized macular to confluent light brown pigmentation which developed nine months ago. The child had been fretful, and the mother had given him ½ tablet of "ex-lax." The following day a generalized eruption appeared, which was followed by the present eruption. It is less prominent on the face and upper part of the trunk than when first seen, six months ago. About two weeks ago the child showed a few papulourticarial lesions scattered on the trunk and face. The lesions do not show wheals after rubbing them.

Biopsy has not been permitted. The results of scrapings were negative for fungi. There has been intermittent use of a mild ointment containing salicylic acid.

DISCUSSION

DR. E. WILLIAM ABRAMOWITZ, New York: Tissue from the affected areas should be examined microscopically for the presence of mast cells to exclude urticaria pigmentosa. The question of an eruption from phenolphthalein or urticaria pigmentosa came up in connection with a case recently presented by Dr. Frank Fraser (ARCH. DERMAT. & SYPH. **40**:512 [Sept.] 1939) before the New York Dermatological Society. Several biopsies showed only scattered mast cells, not sufficient to warrant labeling the condition urticaria pigmentosa. Phenolphthalein and other drugs were ruled out as a cause. Another recent instance of an acquired pigmentation over the eyelid brought up the question of a phenolphthalein eruption or argyria. A drug eruption was finally excluded. Dr. Satenstein, after a study of a cutaneous section in the latter instance, thought that the condition might be a nevus of the mast cell variety. Andrews in his textbook on cutaneous diseases reports on a nursing infant with a fixed eruption thought to be due to phenolphthalein ingested by the mother; however, as it is known that free phenolphthalein is not excreted in mothers' milk (Fantus, B., and Dyniewicz, J. M.: *Am. J. Digest. Dis. & Nutrition* **3**:184 [May] 1936), it is questionable whether the eruption was due to the drug. I have never seen an eruption from phenolphthalein in an infant. There is no other report of such a case in the literature.

DR. HOWARD FOX, New York: At first glance the eruption would appear to be urticaria pigmentosa, but, as Dr. Abramowitz has pointed out, there are several points against this diagnosis. In the first place, there has been no formation of wheals on rubbing the lesion, and I failed to observe any today. In the second place, the lesions tend to coalesce and form fairly large patches, a tendency I do not recall having observed in urticaria pigmentosa. In that disease the lesions, whether small or large, are entirely discrete. In the third place, there is definite history of ingestion of a preparation containing phenolphthalein. Dr. Abramowitz and I should be able to recognize an eruption due to phenolphthalein as he and I

independently described the first case. He is entitled to the chief credit, as he proved the diagnosis by subsequently giving the patient more of the drug (Abramowitz, E. W.: *J. Cutan. Dis.* **36**:11 [Jan.] 1918).

DR. ROBERT L. GILMAN, Philadelphia: Regardless of the diagnosis in the case of this partciular infant, I believe that the pigmentation is excessive either way. I noted too that the mother has decided chloasma.

DR. HARTHER L. KEIM, Detroit: It might be informative if Dr. Mitchell could have the child brought back and give him a small amount of phenolphthalein.

Xanthomatosis (Schüller-Christian Disease). Presented by Dr. Donald S. Mitchell, Montreal, Canada (by invitation).

In A. S., an undernourished-appearing child of 12 years, a fairly profuse eruption of small yellowish papules developed on the face, trunk and arms three years ago. There had been polydipsia, polyuria and loss of weight for several months previous to the eruption.

Investigation showed a urinary output of 10,000 to 12,000 cc. daily, with a specific gravity of 1.000 to 1.002. There was 211 mg. of cholesterol per hundred cubic centimeters of blood. A roentgenogram of the skull showed an area of rarefaction in the right parietal region, "which did not have the usual appearance associated with xanthoma," according to the interpretation. All other examinations gave normal results. Histologic examination showed typical xanthoma, with considerable inflammatory infiltrate.

DISCUSSION

DR. FRED D. WEIDMAN, Philadelphia: I doubt that there is a sufficiency of items to establish this condition as Schüller-Christian disease. There is no history of exophthalmos or jaundice. The only item in support is the fact that there was some prenatal defect. In the literature there is a report of a case (Herzenberg, H.: The Skeletal Form of Niemann-Pick Disease, *Virchows Arch. f. path. Anat.* **269**: 614, 1928) in which there were cholesterosis and defects in the membranous bones, which was regarded as a case of multiple myelomatosis with a superimposed xanthomatosis. In sections of tissue from the patient presented here the histologic picture is unusual indeed. The cells are remarkably large, clear and definitely outlined. The nuclei are apparently huge. When I first saw the sections I thought of the case of neurocytoma which Drs. Montgomery and O'Leary presented two years ago. I suggest that studies be prosecuted further to determine whether the conditions in the 2 cases could be the same or, if not, to determine whether this condition is possibly a disease fundamentally of the blood-forming tissue. Some special primitive type of cell may be at fault, perhaps a plasmoblast. I was not satisfied with the foaminess of these cells. The cholesterol of the blood measured only 211 mg. per hundred cubic centimeters, which is not particularly high.

DR. PAUL A. O'LEARY, Rochester, Minn.: I agree that there are some clinical features in this case that resemble those in the case of neurocytoma or neuroganglionoma that Dr. Hamilton Montgomery and I reported several years ago. The patient does not present any evidence of Schüller-Christian disease at this time but rather presents the picture of multiple xanthomatosis or disseminated xanthomatosis. The finding of normal values for fat and lipoid in the blood does not exclude the possibility of xanthomatosis, because in the disseminated form of xanthomatosis normal values have been obtained on numerous occasions. I favor a diagnosis of disseminated xanthomatosis and urge further study of the histologic material in an effort to establish the diagnosis. There have been varying degrees of success in the treatment of patients with this condition by placing them on rigid ketogenic diets.

DR. DONALD S. MITCHELL, Montreal, Canada (by invitation): In looking up the literature I found a suggestive idea in an extensive article (Warkany, J., and

Mitchell, A. G.: Diabetes Insipidus in Children: A Critical Review of Etiology, Diagnosis, and Treatment, with Report of Four Cases, *Am. J. Dis. Child.* **57**:603-666 [March] 1939) on types of diabetes insipidus classified according to associated conditions. One type was that associated with xanthoma which, the authors stated, usually constitutes part of the Hand-Schüller-Christian syndrome.

Hypodermic Sarcoid. Presented by DR. J. F. BURGESS, Montreal, Canada.

L. L. L., a white man, presents a large bluish red inflammatory tumor, the size of an orange, on the inner aspect of the middle third of the left thigh. According to his history, he first noticed the lesion eight months ago, and since that time it has progressively enlarged. His general health is good. He said that tuberculosis of the kidney developed in his daughter in 1913, after the drinking of nonpasteurized milk, and that some years later she had a tuberculous osteitis of the hip, with a discharging sinus which has never healed and which is draining at the present time. His reaction to tuberculin with dilutions of 1:1,000, 1:10,000 and 1:1,000,000 was strongly positive.

Histologic examination showed numerous rather well demarcated areas containing many lymphocytes and epithelioid cells in the upper part of the cutis, while deeper down there were nests of epithelioid cells and some giant cell formation.

Suggestions as to treatment are requested.

NOTE.—Total excision was performed shortly after the meeting.

DISCUSSION

DR. PAUL E. BECHET, New York: The tumor-like growth on the left thigh is raised and vegetating. It occurs on the site of a biopsy wound done several months ago. I should under these circumstances suspect malignancy. I should suggest surgical excision of the tumor mass, as though it were definitely malignant, and then a histologic examination of the excised material.

DR. GEORGE C. ANDREWS, New York: The clinical appearance of the lesion is not typical of sarcoid, and although I am no specialist in histology, certainly I thought that the microscopic appearance was more typical of mycosis fungoides. I should like to suggest that the condition is the d'emblée type of mycosis fungoides. The clinical appearance of the plum-colored lesion suggests some lymphoblastic process, and the short duration of the tumor growth, I think, is uncommon in sarcoid. I suggest roentgen therapy.

Hypodermic Sarcoid. Presented by DR. J. F. BURGESS, Montreal, Canada.

S., a white man aged about 45, presents brownish red, rather glazed crescentic and oval thickened inflammatory areas on the forehead and forearms, which appeared three months ago. This is his third attack of exactly the same clinical process, the first having been in 1929 and the second in 1932, which lasted two years. His case was investigated during the second attack, and the aforementioned diagnosis was made. No foci of infection were found after a thorough check-up, and roentgenograms of the bones of the hands and feet were normal. There was no history of the ingestion of drugs. The blood smear was normal. The Mantoux reaction was negative with dilutions of 1:1,000, 1:10,000 and 1:1,000,000. The Wassermann reaction of the blood was normal. Numerous forms of treatment were tried, and the eruption eventually cleared up with gold therapy. Further investigations during the present flare-up gave similar results.

Histologic examination in April 1939 showed extensive inflammatory changes in the upper half of the corium. The epidermis was irregularly acanthotic, with some spongiosis and vesiculation. The corium showed a generalized infiltrate of small round cells, with numbers of plasma cells. The blood vessels were dilated

and perhaps increased in number. A second section, taken one month later, showed a similar picture, with an infiltrate made up almost wholly of lymphocytes and a few polymorphonuclear leukocytes.

DISCUSSION

DR. ERWIN P. ZEISLER, Chicago: I think that because of definite nodules in the ears and the glabella and other nodular lesions, I should rule out leprosy. Stains for acid-fast bacilli should be made.

DR. RICHARD S. WEISS, St. Louis: When I first looked at this patient, I thought of leprosy, but on examining more carefully I think that could be ruled out. There is no enlargement of the ulnar nerve, and there are no areas of anesthesia. When I studied further, however, it seemed to me that he presented leukemia of the skin, and I thought the observations on the histologic section bore that out. I have encountered 1 or 2 cases in which the ears were affected, just as were the areas about the eyebrows. I think the condition in this case may turn out to be a leukemia.

Fig. 3 (S.).—Hypodermic sarcoid.

DR. F. E. SENEAR, Chicago: I at first had the same feeling that Dr. Zeisler expressed, that this was a case of leprosy, and, unlike Dr. Wise, I thought that there was definite enlargement of the ulnar nerve on the left side. On considering the remainder of the clinical picture, however, I did not feel that anything else could be determined to support that diagnosis. I think Dr. Zeisler suggested that the patient be thoroughly investigated from that standpoint.

DR. J. F. BURGESS, Montreal, Canada: I shall certainly investigate the condition as to the possibility of its being leprosy. I shall also have further examinations of the blood done from the standpoint of possible leukemia.

NOTE.—Studies have revealed no evidence of leprosy, and complete blood counts and smears have shown no suggestion of leukemia.

Atopic Eczema with Bilateral Cataract. Presented by DR. DONALD S. MITCHELL, Montreal, Canada (by invitation).

A. H., a man aged 22, presents erythematosquamous lichenified and at times exudative eczema of most of the body surface, especially that of the face and neck and over the flexors.

There was a generalized eruption from the age of 3 to 7 years, and the present condition has existed since he was 15. Asthma has been present since the patient was 10 years old, which is worse in the winter and at night but better when he smokes cigarets. His vision was good in both eyes prior to the spring of 1937, but at that time vision in the left eye became poor. In December 1937 the right eye became affected suddenly, and the vision of the left eye then seemed to be improved.

His tonsils and adenoids were removed in 1932. The sinuses are clear. Cutaneous tests and a general investigation showed no abnormal results. Treatment has been symptomatic.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: Cataract is held to be a rare complication of atopic dermatitis, but if careful examination is made with a slit lamp evidence of incipient cataract can sometimes be detected in the form of postcapsular opacities even before there are clinical symptoms of blurring of vision. At the clinic 35 cases of cataract in association with atopic dermatitis have now been observed. In 8 of the cases there was no record of treatment with roentgen rays. This is important from a medicolegal standpoint, as roentgen rays have been incriminated as a factor in the production of cataracts. In most instances in our experience the condition has occurred in patients in their twenties; the youngest patient known to have the condition being 15 (possibly there was one aged 8 years). In the ophthalmologic literature there is mention of a form of hypersensitivity to lens protein. Other theories, such as Dr. Goeckerman's of a form of avitaminosis, deserve careful scrutiny, but so far no satisfactory explanation has been advanced to account for the formation of cataracts in these cases.

DR. JACOB HYAMS SWARTZ, Boston: In a group of patients with atopic dermatitis at the Massachusetts General Hospital there were about 10 with cataracts, and the ophthalmologic report was "deficiency type of cataract." As Dr. Brunsting has stated, the age in these cases is usually 15 or above. I believe that perhaps restriction of the diet from infancy on may be the causative agent.

Mycosis Fungoides. Presented by DR. BARNEY B. USHER, Montreal, Canada (by invitation).

U. L., a man aged 38, was first seen one year ago for fleeting attacks of dermatitis. Large plaques of scaly dermatitis soon appeared with paroxysms of severe pruritus, which gradually became infiltrated and indurated with tumorous development. Sites of predilection were the lateral aspects of the trunk and upper extremities. There was no adenopathy. Hematologic examination showed moderate lymphocytosis and moderate monocytosis and a slight increase in the rate of sedimentation. Histologic examination showed isolated columns and masses of cells, lying in the upper layers of the corium and extending downward into the deeper layers. These aggregates of cells were remarkable because of their variegated appearance. Within such aggregates large numbers of eosinophilic polymorphonuclear leukocytes were encountered. There were considerable numbers of endothelial cells, small numbers of lymphocytes and considerable numbers of pale cells with vesicular nuclei that in many respects resembled endothelioid cells except that the cytoplasm was slightly different. Small numbers of fibroblasts were encountered, and a few capillaries were seen in such aggregates of tissue. No giant cells of any type were encountered except that in some situations there were agglomerations of endothelioid cells which give pseudogiant forms. There was no necrosis or exudation. The masses of exudate were irregular in size and varied in distribution, the major portion being in the upper layers of the corium but extending in fairly well defined masses into the deeper layers. Cellular detritus was not prominent in these collections of cells.

Administration of sulfanilamide, 30 to 60 grains (2 to 4 Gm.) daily for two months, resulted in almost complete healing of the condition. There was a recur-

rence when the drug was stopped. No improvement was noted under sulfapyridine therapy but rather a return to the original state. There was improvement when sulfanilamide therapy was resumed.

Eczema Seborrhoeicum. Presented by Dr. Donald S. Mitchell, Montreal, Canada (by invitation).

J. P., a man aged 38, foreign born and of the long unemployed laboring type, presents a chronic recurrent erythematous and exudative, and at times psoriasiform, eruption on the scalp, face, ears, eyelids and flexures, of six years' duration. There has been an intermittent folliculitis of the bearded region and furunculosis of various parts of the body.

Yeastlike forms were observed on direct examination on one occasion. Cultures have yielded only staphylococci. Complete physical and laboratory examinations have shown nothing abnormal. Histologic examination showed decided acanthosis with long tonguelike projections. Along a hair, at the surface and extending down along it a short distance, there was a polymorphonuclear leukocytic reaction. Surrounding this and about the follicles and blood vessels there was an intense infiltrate of plasma and round cells. In the interstitial tissue there was less cellular reaction and some connective tissue reaction.

Treatment with various ointments and lotions, dyes, roentgen rays, staphylococcus toxoid and foreign protein has been only irregularly helpful.

DISCUSSION

Dr. E. William Abramowitz, New York: I understand from Dr. Usher that a congo red test was done a year ago and the result was negative. I suggest that it be repeated because the lesions on the legs resemble a local amyloidosis of the skin.

Dr. J. H. Mitchell, Chicago: In this type of case I am not able to arrive at any opinion without a great deal of work in the way of cultures and microscopic studies. The numerous follicular infections rather suggest a staphylococcic infection. Of course, the staphylococcus and the streptococcus possibly coexist. The lesions about the canal of the right ear are suggestive of a streptococcic infection, but the lesions in the axillas are hardly of the "open book" type. The fissuring is typical on the soles.

Dr. Samuel Ayres Jr., Los Angeles: This case closely resembles several I have encountered in the past two or three years, in which there have been a follicular pustular infection, blepharitis and a seborrheic type of lesion in the axillas, face and scalp and sometimes in the genitocrural region. At times the lesions on the face are definitely follicular, resembling sycosis vulgaris, and at other times they look like lupus erythematosus. Because of the fact that the seborrheic and pustular lesions would at times give place to erythematous lesions on the face suggestive of lupus erythematosus, gold therapy was used in several cases and fairly good results were apparently achieved. I think the condition in the case being presented is most recalcitrant. There is undoubtedly something in the background besides a follicular infection, even though that factor has not been encountered in this type of case.

Dr. E. William Abramowitz, New York: I think that we have all had trouble in treating this type of dermatosis. I would suggest 30 per cent sulfur in petrolatum to be applied once or twice daily. I have found this to be effective.

Kaposi's Sarcoma. Presented by Dr. Donald S. Mitchell, Montreal, Canada (by invitation).

L. L., a thick-set Italian aged 44, presents thickened infiltrated inflammatory plaques and nodules of ten years' duration on the ears, nose, hands and feet.

The first histologic examination, made four years ago, showed a patchy lymphocytic infiltration scattered through the corium, with more about the vessels and glandular structures.

Section made a year later showed typical angiosarcoma. Injections of an arsenical compound have been used. The lesions have been kept under control

mainly by high voltage roentgen therapy. In 1938 an acute abscess developed on the foot, with fever, necessitating hospital care for two months, after which many of the lesions flattened considerably and some seemed to have entirely disappeared.

DISCUSSION

DR. HIRAM E. MILLER, San Francisco: A patient was presented at the meeting of the American Dermatological Association in San Francisco ten or more years ago with many lesions of angiosarcoma of Kaposi on his feet, hands and ears. About seven years ago a severe streptococcic infection of the upper part of the arm

Fig. 4 (B. H.).—Pemphigus (Senear-Usher syndrome).

developed, with fever (temperature of 106 to 107 F.) for a considerable time. Two months later the lesions of Kaposi's sarcoma began to disappear, and in five months they were entirely gone. That was six years ago, and he is still entirely free of the disease.

Pemphigus (Senear-Usher Syndrome). Presented by DR. BARNEY USHER, Montreal, Canada (by invitation).

B. H., a man aged 33, presents greasy scales in the scalp, demarcated crusted inflammatory lesions on the cheeks and nose and crusted areas on the back and axillas, with bullous formation predominating. The duration of the eruption is eighteen months. Otherwise his condition is normal.

Histologic examination of an early lesion showed a small corner of a bulla, the roof being mostly missing. The base showed ragged epidermis varying in thickness and missing in places. There was edema of the papillary part of the corium and the epidermis, with little vascular dilatation and polymorphonuclear exudate about the vessels, some of the cells streaming into the epidermis. The middle and lower parts of the corium showed little change except some exudate of round cells about the fixed structures. A section of an older lesion showed acanthosis with a diminished granular layer and only a little scaling. There was an infiltrate, intense about the vessels, in the papillary portion of the corium, made up chiefly of lymphocytes, with an occasional polymorphonuclear leukocyte and plasma cell. At one site the epidermis was thinned and flattened, with cellular infiltrate beneath. The lower part of the corium showed only moderate edema.

Treatment consisted of injections of a gold preparation, a high vitamin diet, administration of mixed vitamins by mouth and local application of sulfur and tar. No improvement was noted.

DISCUSSION

DR. OLIVER S. ORMSBY, Chicago: My impression is that the condition is pemphigus, but not the erythematodes variety. In this form of pemphigus the eruption resembles lupus erythematosus of the nose and cheeks, while on the chest and back the lesions resemble seborrheic eczema and in addition there are bullous lesions of the pemphigus type. The lesions therefore present the clinical features of lupus erythematosus, seborrheic eczema and pemphigus. The patient had a rather generalized eruption consisting of flaccid bullae together with an exfoliative dermatitis, which is characteristic of the foliaceus variety of pemphigus rather than the erythematodes type.

DR. BARNEY USHER, Montreal, Canada (by invitation): In the initial phase of the disease, the patient presented what appeared to some of those who saw him to be seborrhea of the scalp, with scaling and greasiness. Then a bat wing–shaped lesion developed on the bridge of the nose, which persisted for some months, and in the last few months there has been a gradual development of a bullous eruption on the body. The initial lesion was that of seborrheic eczema, impetiginous in parts. Only in the past few months has the pemphigus foliaceus eruption developed.

NOTE.—The patient died two weeks after the presentation, apparently of a septicemia. Staphylococci were obtained from the blood at necropsy.

Prurigo (Hebra). Presented by DR. BARNEY USHER, Montreal, Canada (by invitation).

N. E., a man aged 57, born in Galicia, presented a papulourticarial lichenified eruption on all the extremities and lower half of the trunk. The older lesions are intensely lichenified and in places nodular. There are increasing pigmentation and intense pruritus. The condition was first noted eight years ago, since which time he has been on a "relief" diet, decidedly deficient in vitamins. Beggar's psychologic neurosis was diagnosed by the neurologist. Chemical examination of the blood and hematologic examination gave normal results. There were no foci of infection, and the basal metabolic rate was normal. Histologic examination showed a surface covered by keratinized stratified squamous epithelium in which only a few minute foci of parakeratosis were seen. In one place in the epidermis there was a small vesicle filled with partially degenerated epithelium. The papillary layer of the cutis was edematous, showed a slight proliferation of connective tissue cells and was focally infiltrated by lymphocytes and round cells. The deeper layers of the cutis were moderately edematous, and the edema was most evident in the perivascular region. In the perivascular areas infiltrations of round cells and lymphocytes were observed, but no plasma cells or eosinophils. The deeper layers showed a number

of sweat glands, which were not remarkable. Sections stained with congo red showed no amyloid. No change was noted after intradermal injections of congo red.

Treatment consisted of administration of a high vitamin diet and calcium, ultraviolet irradiation, roentgen therapy and application of Unna's paste. No change was noted in consequence.

Radiodermatitis. Cellular Keloid? Presented by DR. J. F. BURGESS, Montreal, Canada.

N. McL., a white woman aged 30, had roentgen ray therapy in 1926 for hypertrichosis of the chin. She was seen first in 1930, when there were ulceration on each side of the chin and marginal telangiectasia and atrophy. These conditions healed after eight months. In 1937 she presented a tumor the size of a marble on the left side of the chin, which was thought to be an epithelioma but was not ulcerated. It was desiccated, and radium was applied. Healing resulted, but three

Fig. 5 (N. McL.).—Roentgen ray sarcoma.

months later there was a recurrence. A biopsy was performed at that time, and the following report was made:

The histiologic section showed a cellular fibrous tissue covered by a layer of epidermis devoid of papillae. The cells were spindle shaped with intervening collagen which in places was edematous. There were a few endothelium-lined vascular spaces, which did not contain any blood. At the base of the section there was a small area of more normal zona reticularis. There was an overgrowth of cellular fibrous tissue on the upper part of the skin, covered directly by epidermis devoid of papillae.

In July 1938 the tumor, the size of a tangerine, was removed surgically, and skin was grafted. Recurrence was again seen at about the same area. It was thought that the tumor was attached to the bone. A roentgenogram of the mandible showed some decalcified areas in the region underlying the growth. The tumor was again desiccated and destroyed down to the surface of the bone in February 1939, with a recurrence within two months.

The case is presented for an opinion as to diagnosis and further form of treatment.

DISCUSSION

DR. ERWIN P. ZEISLER, Chicago: I should like to offer the diagnosis of sarcoma. I think the rapidity of recurrence is inconsistent with the diagnosis of keloid. The histologic observations also could be interpreted as those of a neurogenic sarcoma. The problem of therapy is a difficult one. This type of sarcoma recurs unless widely removed surgically, and it is radioresistant. I suggest interstitial radium therapy.

DR. J. F. BURGESS, Montreal, Canada: The histologic diagnosis was benign cellular tumor. After following the case for a time and noting the great tendency of the condition to recur, I feel that it must be considered clinically a malignant growth. I propose to have the patient observed by a competent surgeon, with a view to widespread and total removal.

NOTE.—Shortly after the meeting the patient was admitted to the hospital, wide excision was performed and the operation was followed by electrocoagulation, which involved the bone, after stripping of the periosteum, and resulted in partial necrosis of the bone. Subsequent histologic studies showed that while in some areas keloidal change predominated, in others the sarcomatous nature of the growth was revealed. The pathologist's diagnosis was roentgen ray sarcoma. In September a wide area of bone sloughed away. In October three separate pea-sized reddish brown papules appeared about the original site of the growth.

Hemolytic Jaundice with Ulceration of the Skin. Presented by DR. J. J. MCGOVERN, Westmount, Quebec, Canada (by invitation).

S., a white man aged 23, has been under observation for two years on account of recurrent indolent multiple ulcers of both legs which have been refractory to treatment.

Investigation showed a negative Wassermann reaction, a basal metabolic rate of —1 per cent, with a normal roentgen picture of the blood vessels of the legs. The hemogram of September 1938 showed the sedimentation rate to be moderately accelerated, with a moderate shift to the left of neutrophils. There was evidence of a toxic condition.

In May 1939 there was a slight macrocytic hypochromic anemia, with a decided leukocytic shift to the left. The type of anemia with abnormal fragility of the cells corresponds with a clinical diagnosis of hemolytic jaundice.

A barium sulfate enema showed that the splenic flexure was displaced medially by the spleen, which was enlarged.

A histologic section was made of a portion of skin in the center of which was an ulcer with necrotic inflammatory exudate on the surface. The epidermis on either side was normal and dipped down slightly at the margin. The base of the ulcer was hemorrhagic, the hemorrhage having separated the tissue which appeared as bundles of connective tissue carrying blood vessels, most of which showed endothelial hypertrophy and about which were proliferation of large endothelial cells and infiltration with lymphocytes and plasma cells. Beneath this the area of dense scar tissue was also infiltrated with lymphocytes, plasma cells and a few eosinophils, particularly about the blood vessels. Some of the arteries showed thickening of the walls and compression of the lumen. Some showed hyaline degeneration. Scattered throughout were phagocytes containing blood pigment. The lesion appeared to be a chronic ulcer showing marked fibrosis at its base and extensive recent hemorrhage.

The treatment recommended was splenectomy.

DISCUSSION

DR. DUDLEY C. SMITH, Charlottesville, Va.: I should like to suggest the possibility of sickle cell anemia in this case. Routine blood smears may not show the sickle-shaped or crescentic red cells, but they can be demonstrated in a hanging drop of blood. This condition and other kindred diseases of the blood may cause chronic ulcers. A few cases have been reported in the white race.

DR. C. L. CUMMER, Cleveland: I should like to ask whether the patient has shown icterus at any time. I do not note any jaundice today.

DR. J. J. MCGOVERN, Westmount, Quebec, Canada (by invitation): The patient for the past two years has suffered from chronic ulcers of the lower part of the legs. The ulcers would improve while he was at rest in the hospital with the legs raised, but when he was allowed on his feet they broke out again. Investigations showed that they were not varicose, tuberculous or syphilitic ulcers. Attention was directed to an article (Taylor, E. S.: Chronic Ulcer of the Leg Associated with Congenital Hemolytic Jaundice, *J. A. M. A.* **112**:1574 [April 22] 1939) that gave us a clue. The hemogram on two occasions showed increased fragility of the red cells. The report of the van den Bergh test on two occasions was: direct, delayed; indirect, positive: 2 units and 1.5 units, respectively. The bleeding time was one and three-tenths seconds. The histologic diagnosis was nonspecific chronic ulcer. A barium sulfate enema revealed the splenic flexure displaced toward the midline by the spleen, which was thought to be enlarged. An icteroid tint of the scleras was observed two or three times. By the process of elimination, the conclusion is forced that the condition is a chronic ulcer of the leg due to hemolytic jaundice.

There have been altogether, according to the article in *The Journal*, 17 cases reported in the literature, mostly in Germany and in Scandinavian countries. The treatment recommended is splenectomy.

DR. GEORGE M. LEWIS, New York: The punched-out appearance of these ulcers and the history the patient gives of itching and traumatization due to it, with the absence of palatal reflexes, would suggest dermatitis factitia.

DR. J. J. MCGOVERN, Westmount, Quebec, Canada (by invitation): In answer to the question as to whether the lesions could be self inflicted, I may say that some time ago the leg was put in a boot of Unna's paste (hard paste of zinc oxide N. F.), which covered the ulcer completely. When the boot was removed, three or four weeks later, the ulcer had increased considerably in size. This, I feel, rules out the possibility of factitial dermatitis.

DR. F. E. SENEAR, Chicago: A replica of this picture of ulcer of the leg was recently observed in a patient with sickle cell anemia and again during the past month in a patient with Cooley's anemia, associated with extreme fragility of the red cells. In a recent issue of *The Journal of the American Medical Association* attention was called to the type of ulcer of the leg shown today by Dr. McGovern in association with Cooley's anemia. It is obvious that if one considers anemia as an explanation for old chronic ulcers on the leg, particularly in young persons, the opportunity of studying a most interesting new group in dermatology will be provided.

DR. FRED D. WEIDMAN, Philadelphia: I agree that there is a possibility of factitial dermatitis. However, Dr. Ketron will shortly read a paper before the American Dermatological Association, Inc. (Ketron, L. W.: Cutaneous Manifestations of Periarteritis Nodosa, ARCH. DERMAT. & SYPH. **40**:929 [Dec.] 1939) on periarteritis nodosa, and I invite the members to keep in mind the picture of this patient at that time. In the sections there is evidence of definite vasculitis and perivasculitis. The condition under discussion is not true periarteritis nodosa, but I think that some of the members may have read a recent article on polyarteritis nodosa describing conditions which resemble this one. The fleeting jaundice may be due to toxic hemolysis; it was stated in the history that there was evidence of a toxic condition. I do not know whether this man has vasculitis or not, but in any event the possibility of periarteritis should be investigated. The age of the patient is against this diagnosis, since patients generally do not live as long as this man has.

DR. F. E. SENEAR, Chicago: I was referring particularly to the type of ulcer shown in the photograph in Dr. McGovern's case and not to the small lesions disseminated over the legs generally.

NEW ENGLAND DERMATOLOGICAL SOCIETY

FREDERICK S. BURNS, M.D., *President*

BERNARD APPEL, M.D., *Secretary*

Boston, Feb. 8, 1939

Myositis Ossificans. Presented by DR. BERNARD APPEL, Boston.

In 1924 this patient, a 37 year old Negro choreman, had a crushing injury of his left thigh, with avulsion of skin and muscle tissue. The area healed with formation of a keloidal scar. About three months ago the center of the scar broke down, and an ulcer resulted, from which spicules of bone protruded.

The patient repeatedly showed a positive Hinton reaction and is now receiving active antisyphilitic therapy. There is no clinical evidence of either early or late active syphilis.

Examination shows an ulcerated area 2 inches (5 cm.) in diameter in the middle of the lateral aspect of the left thigh. This is located in the center of a long band of keloidal scar tissue extending from the upper part of the thigh to a point several inches below the knee. There are many spicules of bone protruding from the ulcerated area.

Roentgen examination showed typical myositis ossificans.

DISCUSSION

DR. WILLIAM P. BOARDMAN, Boston: Two or three questions arise in this case. The man probably has syphilis. Whether the present condition has anything to do with the syphilis or not is a question, but treatment does not seem to have modified it in the short time that he has been treated. The other thing is that the area in which the scar is broken down and the bony spicules are found is that in which he received roentgen and radium therapy some years ago, which healed the original traumatic ulcer. Whether that has anything to do with the formation of these bony spicules I do not know. A roentgenogram of the knee was taken, which did not show any such spicules lower in the scar. This would seem to indicate that the roentgen rays and radium had something to do with the origin of this trouble.

In regard to treatment, it seems that wide excision of that part of the scar might be of benefit, although if the process is going on and gradually involving the whole scar, excision of that part of it would do no good.

DR. FRANCIS M. THURMON, Boston: I should like to suggest fever therapy as supplementary to the antisyphilitic treatment.

Mycosis Fungoides. Presented by DR. C. GUY LANE, Boston.

Six years ago this 62 year old man noticed mild scaling and pruritus of his legs which persisted in spite of therapy and gradually spread to involve the entire body. Approximately eight months ago severe pruritus developed and was accompanied by formation of nodules, which increased in size, ulcerated and became necrotic. There is now generalized involvement of scaling, tan-brown and deep red plaques of various shapes and configurations. Scattered over the trunk are crescent-shaped deep brown raised scars. On the abdomen, left thigh and left knee five tumors are present, varying from 2 to 6 cm. in diameter, which are fungating and the centers of which are necrotic.

The white blood cell count was 9,000 per cubic millimeter, with polymorphonuclears 76 per cent, lymphocytes 16 per cent, mononuclears 4 per cent and eosinophils 4 per cent.

DISCUSSION

DR. E. W. ABRAMOWITZ, New York (by invitation): I think it is a case of fairly typical granulomatous disease.

DR. BERNARD APPEL, Boston: I should like to call attention to a report recently submitted of the apparent cure of mycosis fungoides in 5 or 6 of 8 cases by intramuscular injections of chaulmoogra oil esters and to state that I have tried such therapy in 1 case. Unfortunately, the patient had too advanced a condition and died of bronchial pneumonia before I had a chance to give her many injections, but there was apparently slight improvement in the symptoms after six injections. I think chaulmoogra oil may be of some value.

Actinomycosis. Presented by DR. C. GUY LANE, Boston.

This 39 year old man has had a dermatitis and swelling of the entire right side of his face since June 1938. At that time he noticed a swelling of the right cheek, which within three days thereafter reached its present size. A week after the onset small pustules appeared over the surface. The only growth noticed since is a slight downward enlargement. The patient is a roofer. He does not come in contact with animals or with hay, but he puts nails in his mouth and has been having his teeth extracted during his present illness.

The swelling at present extends upward to the zygomatic arch, impinges on the loose tissue of the lower lid and extends backward over the ramus of the mandible and into the submaxillary area. There is woody induration, and the overlying skin is taut and deep brown. Scattered over the surface are many pustules and areas of scar retraction.

Pus obtained by aspiration from one small fluctuant area contained many small round yellowish granules which were identified as actinomycotic and which are growing anaerobically. Microscopic examination showed chronic inflammation. One positive Hinton reaction, four negative Hinton reactions and one negative Laughlen reaction were reported after examination of the blood.

Treatment has consisted of thymol, 1.5 Gm., three times a day on two of every three days. The superficial pustules have disappeared and infiltration around the eye has subsided, but there is no change in the greater portion of the lesions.

DISCUSSION

DR. J. H. SWARTZ, Boston: When the case was first presented at one of the staff meetings, I was opposed to the diagnosis of actinomycosis because of the firmness of the lesions, and it looked to me more as though there were involvement of the parotid gland, but after a while, as the lesions were dressed, I saw definite discharging abscesses, and by Dr. Ray's microscopic demonstration the diagnosis was definitely established. I feel that in this case ethyl iodide would be of value.

A Case for Diagnosis (Lupus Erythematosus? Lichen Planus?). Presented by DR. MAURICE MYER TOLMAN, Boston.

This 28 year old man is exposed to the sun a great deal. Two or three years ago lesions appeared on his lips, but there was no definite relation to sunburn. These have been slowly increasing in size, and at present there are red, scaly leukoplakia-like lesions on both lips, with an elevated circinate border which shows definite stippling above and just beyond the vermilion border. The tip of the nose seems erythematous, and there is greater than normal prominence of the follicles.

Treatment has consisted of intramuscular bismuth subsalicylate.

DISCUSSION

DR. AUSTIN W. CHEEVER, Boston: I favor a diagnosis of lupus erythematosus. It does not seem to me that the lesions inside the mouth are consistent with a diagnosis of lichen planus. I am wondering, since most of them are on the right side of the mouth, whether the gold teeth on that side have something to do with

the process. The pattern inside the mouth is rectangular and fits pretty well the impressions made by the teeth.

DR. FRANCIS M. THURMON, Boston: I should like to suggest the diagnosis of a resistant, slowly growing benign epithelioma.

DR. J. H. SWARTZ, Boston: I think, since the diagnosis has been offered, I favor lichen planus, particularly for the lesion on the lower lip. The lesions are discrete. As one looks at them closely, they have an umbilication, and the color on the lower lip is suggestive of lichen planus. The lesion on the upper lip, I admit, is not as definite and would fit in perhaps with the picture of lupus erythematosus. In correlation with a study of each lesion, the primary lesions and the development of the process, I believe that microscopic examination would probably show lichen planus.

DR. C. GUY LANE, Boston: It seemed to me, in looking at these lesions carefully through the lens, that there was enough evidence to warrant a diagnosis of lichen planus. If one examines the lower border of the lesion on the lower lip, there are definite small annular lesions. They have a little pearly ring and a little umbilication which shows well with the lens, and I think part of the lesion has a suggested linear arrangement which compares well with what one sees as Wickham's striae in other lesions of lichen planus. The same holds true of the lesion in the middle of the upper lip, particularly above the upper limit of the vermilion border, where there is a definite annular lesion, again with a fine whitish or pinkish line around the periphery. I think that in this lesion also there are areas characteristic of Wickham's striae.

Lupus Erythematosus. Presented by DR. C. GUY LANE, Boston.

Three months ago this 21 year old woman noticed a small brown raised area on her left cheek; it slowly spread peripherally, leaving the center shining and clear. No treatment was given, and several other such areas appeared spontaneously. New and old lesions are now present on both cheeks. The new lesions consist of bean-sized brown maculopapules the border of which blends into the normal skin. The oldest lesions consist of circular areas approximately 3 cm. in diameter with slightly raised borders and smooth, shining atrophic centers in which are seen many dilated, plugged follicles.

Microscopic examination suggested lupus erythematosus.

DISCUSSION

DR. J. H. SWARTZ, Boston: The appearance of the pathologic section is not against the diagnosis of leprosy. Also, in one part of the slide the picture is consistent with lupus erythematosus.

DR. JOHN GODWIN DOWNING, Boston: I do not think the clinical picture is that of lupus erythematosus. First, notice the character of the circular lesions. The ulnar nerve is definitely thickened. The patient was born in Russia and has not been in the United States many years. One cannot dismiss the suggestion of searching for Hansen's bacillus and making sure that there is no possibility of leprosy.

Pemphigus. Presented by DR. C. GUY LANE, Boston.

This 57 year old woman has had chronic lacrimation, a feeling of "mucus in her throat" and recurrent small blisters on her hands and face for three years. One month before admission to the hospital she had a sensation as of a foreign body in her right eye.

The right eye shows considerable symblepharon, especially of the outer canthus and the lower cul-de-sac. The upper lid shows scarring, with considerable thickening and conjunctivitis. The posterior portion of the palate shows linear scarring;

the soft palate and the tonsillar pillars are scarred and adherent to the posterior pharyngeal wall, so that there is only a 0.5 cm. opening from the nasopharynx. There are no cutaneous lesions.

Examination of the sinuses shows thickened mucosa.

Treatment has consisted of injections of pontocaine hydrochloride. Symptomatic improvement has been obtained.

DISCUSSION

DR. E. W. ABRAMOWITZ, New York (by invitation): Dr. J. V. Klauder has had a great deal of experience, and he presented before the Philadelphia Dermatological Society (ARCH. DERMAT. & SYPH. **38**:988 [Dec.] 1938) a series of cases with the diagnosis of essential shrinking of the eye. I think this case falls into that category. I don't know whether the dermatologists will accept this condition as pemphigus in the absence of the lesions that one usually looks for on the body and in the mouth when no conjunctival shrinkage is present, but time will tell.

I remember seeing a condition of this kind in a young boy some years ago (Cohen, M., and Sulzberger, M. B.: Essential Shrinkage of the Conjunctiva in a Case of Probable Epidermolysis Bullosa Dystrophica, *Arch. Ophth.* **13**:374 [March] 1935). The patient had shrinkage of one eye, and it was suggested that he be given potassium iodide. This is exceedingly dangerous. The boy, of course, had a reaction in the involved eye. I do not consider it advisable to use such treatment, but it is interesting to consider, especially with the lesions developing in the back of the throat. I have never seen anything like that before, and I should not think of suggesting the diagnosis of pemphigus unless essential shrinkage of the eye is the same thing as what dermatologists call pemphigus.

DR. E. LAWRENCE OLIVER, Boston: Within the last ten years, in consultation with the physicians of the Eye and Ear Infirmary, I have seen a number of patients with this type of process. One of them had cutaneous lesions (bullae), but most of them showed simply this condition of the eyes, with severe conjunctival adhesions. I think that conjunctival adhesions, especially on the lower lid, are suggestive of pemphigus and that when such lesions are accompanied with oral lesions one can make a diagnosis of pemphigus. I had a private patient who had this condition for three or four years before anything showed on the skin, but later she had an extensive bullous eruption all over the body.

DR. JOHN GODWIN DOWNING, Boston: About one month ago I was asked to see a baby at St. Elizabeth's Hospital. The baby was born by normal delivery, and at birth bullous lesions were noticed on both lips. When the baby cried bullous lesions were noticed on the tongue and on the lower gingiva. When the nurse applied oil on the outer aspect of the arm during the usual cleaning of the skin a bullous lesion arose there; later a series of them appeared on the body, face and extremities. These gradually quieted down. Cultures of material from the lesions were sterile. The child is still living. Most of the lesions in the mouth and most of those on the body have disappeared, but there is still an occasional one on the extremities. The interesting part is that on the right leg, just below the patella, there is a foveated scar at the site of one of the lesions. The first diagnosis was pemphigus neonatorum, but the condition is now believed to have been epidermolysis bullosa.

DR. C. GUY LANE, Boston: I wish to point out that this patient has had other lesions on the skin which were consistent with pemphigus. I think it is proper also to call attention to the results of consultation with oculists and laryngologists. Several specialists in diseases of the eye have seen the patient and have made a diagnosis of pemphigus. Dr. H. P. Mosher saw her and emphasized the fact that similar lesions in the throat may be produced by pemphigus or syphilis.

Scar of Oriental Sore. Presented by DR. C. GUY LANE, Boston.

At the age of 18 months this 35 year old Turkish woman had a boil on her right cheek, which came to a head. The eye was not swollen, although persons

living in her neighborhood with similar lesions did have swollen eyes. The lesion was treated with poultices and incision. The patient lived in Turkey until she was 10 years of age. On the right cheek, below the lateral half of the right eye, there is a rather depressed white scar about 2 cm. in diameter, with a ragged edge. There is no evidence of activity.

DISCUSSION

DR. MAURICE J. STRAUSS, New Haven, Conn.: I know almost nothing about Aleppo boils, but this scar has an unusual appearance. I should like to ask whether this is typical of the scar left by an Aleppo boil or whether that diagnosis was made simply because the lesion occurred in Turkey.

DR. E. LAWRENCE OLIVER, Boston: The patient comes from Harpoot, and she says her mother tells her that practically all of the people there have this disease at some time, usually in childhood. I think the statistics will show that fully 90 per cent have it. I think it is a characteristic scar. When I was in Turkey, many years ago, I saw a large number of persons on the street who had similar scars on the face.

Spontaneous Necrotic Dermatitis (Hemolytic Streptococcus). Presented by DR. C. GUY LANE, Boston.

This 52 year old woman has had arthritis for the past thirty-four years. At the age of 12 she had tuberculous adenitis. In 1914 her tonsils and adenoids were removed, and there was a submucous resection for a discharge. She had a positive Wassermann reaction in 1917, but all the reactions have been negative since. She was admitted to the hospital on Oct. 14, 1938. Fifteen months previously a "pimple" had appeared on her right breast. At onset this had a blue-black appearance, and it soon broke down to form an ulcer. This healed in a few weeks, and another lesion appeared on the left breast in the same manner as the first. This did not heal well and spread peripherally to involve nearly the entire left breast. Under therapy in the hospital it healed in three months. Since then she has had these lesions to a lesser extent in various places. The patient describes two types of lesions: one a small red pinpoint area which appears and disappears equally rapidly; the other blue-black lesions which go on to form small blisters filled with black fluid, which may break down to form small ulcers or go on to form large ulcers, as already mentioned. She has had these on her elbows, buttocks and hands. Three weeks prior to her admission to the hospital one formed on the right ankle, over the internal malleolus. This progressed to ulceration and caused the patient to come to the hospital.

She presents large scarred areas on both breasts and the right internal malleolus and small, sharply circumscribed scars on both buttocks.

The patient was tested with various vaccines and showed a specific necrotic reaction which reduplicated the spontaneous lesions when hemolytic streptococcus vaccine was given intradermally. This occurred in a dilution as high as 1:1,000. Controls did not react in this manner. The patient was also tested with nonhemolytic streptococci, Staphylococcus aureus, staphylococcus toxoid, plain broth, Bacillus coli, Streptococcus viridans, typhoid vaccine and tuberculin. To these various vaccines her reaction did not vary from the normal. Intradermal injection of beta hemolytic streptococcus extract and of the protein and carbohydrate fractions of the streptococcus elicited no abnormal reaction.

Microscopic examination of one of the purpuric areas a few hours old showed "thrombosis of small vessels in the corium, just below the epidermis."

Microscopic examination of an intact necrotic nodule showed "intact epithelium and an area of acute inflammation below it."

DISCUSSION

DR. L. CAPLAN (by invitation): The patient is hypersensitive to hemolytic streptococci. With Dr. Champ Lyons' help two fractions were obtained, the car-

bohydrate fraction and the protein fraction, and unfortunately she did not show in response to either fraction any hypersensitivity greater than the controls. Dr. Lyons said that there are about five fractions in hemolytic streptococci, but those treating her were not able to obtain the other three fractions. She was tested with a nonhemolytic streptococcus and the various other streptococci, and she showed hypersensitivity to hemolytic streptococci with a solution as high as 1 : 1,000.

A Case for Diagnosis (Atrophia Cutis Maculosa?). Presented by DR. JOSEPH MULLER, Worcester, Mass.

About two and one-half years ago the mother of this 15 year old school girl noticed oval white spots on the girl's arms and shoulders. She has never been seriously ill. The menses started at the age of 11, and the periods are regular. There are round and oval lesions from 1 to 2 cm. in diameter in which the skin is thin, depigmented and dry. Other lesions of the same size appear in groups. For the first two months they are slightly raised and pink. Afterward they change to the picture just described.

Treatment has consisted of administration of thyroid, of iron and solution of potassium arsenite U. S. P., without benefit.

Microscopic examination shows enormous thickening of the corium, which, as measured from the sections, is fully 6 mm. in thickness. The epidermis is thin, being two cells thick in one portion of a section and in other places varying from three to four, five, six or eight cells in thickness. There are few changes in the epidermis other than slight hyperkeratosis, atrophy, shortening of the rete cones and some atrophy of the appendages. Beneath the epidermis and in the superficial parts of the corium there is a zone fully 1 mm. wide in which the collagenous fibers are swollen and appear fragmented and gnarled. Between them there is a fine deposit of pink-staining material.* The blood vessels are infrequent in this zone, and those present are surrounded by thin collars of lymphocytes and a few scattered plasma cells. In the deeper part of the corium the collagenous fibers are broad, heavy and enlaced. Only a few fat cells are seen, and these surround the atrophic coils of sweat glands and groups of sebaceous glands. A few fat cells also border the blood vessels. Few nuclei are present in the mass of collagenous tissue. These changes are histologically in keeping with the atrophy of the skin described by Jadassohn under the term "anetodermia erythematodes" and otherwise known as atrophia cutis idiopathica maculosa.

DISCUSSION

DR. MAURICE J. STRAUSS, New Haven, Conn.: This may be a case of benign tumor-like new growths of Schweninger and Buzzi.

DR. E. WILLIAM ABRAMOWITZ, New York (by invitation): I should like to second Dr. Strauss's suggestion. I don't think the picture is entirely the classic one of that disease, but I think that with the other lesions present, even though they do not have the buttonhole depression, it is a form of that condition.

There is another point that I want to speak about, which may be a slight digression. I transilluminated these lesions; they looked like little sebaceous cysts, and they transilluminated very clearly. I have been doing some work with transillumination and examination of lesions and benign cutaneous growths with a useful and inexpensive little instrument which has been of great help to me, especially in connection with melanoma. I am using the term "melanoma" to designate the dark blue pigmented lesion that one ordinarily suspects of being malignant. In transilluminating the various growths I find that cysts and, for instance, this particular lesion are superficial epitheliomas and the light goes right through them, whereas in xanthoma, for instance, hard fibroid tissue will come out rather cloudily. The most important use of transillumination is in the case

of a pigmented growth which has been tampered with, to determine whether the growth should be excised and, if so, to what extent. Transillumination in such a case sometimes shows little opaque dots far beyond the pigmented lesions, indicating that the melanoma is malignant.

DR. E. MYLES STANDISH, Hartford, Conn.: There are two distinct phases of this disease. On the back of this patient the lesions are new, definite, tumor-like, hard and raised, whereas on the anterior axillary borders there are distinct buttonhole-like lesions, about two or three on each side, with definite atrophy. I agree with Dr. Strauss's diagnosis.

DR. ELLWOOD C. WEISE, Bridgeport, Conn.: It is my impression that the tumors of Schweninger-Buzzi disease at first may appear red or may have a bluish tint. At first they are firm. Later, after they undergo further atrophy, some of them possess this soft feeling. On palpation one gets the impression of a herniation through what appears to be a ring at the base of the growth.

I should like to hear from some one on that point (color and consistency at onset), because it is my recollection that the lesions are firm at first and become soft only after the atrophy has progressed.

DR. MAURICE J. STRAUSS, New Haven, Conn.: Perhaps I should not have been so brief, but my reason for suggesting this diagnosis was the presence of lesions in both stages, the tumor-like new growths on the back and the lesions over the front of the arms, which the patient told me were the original lesions and which have undergone an atrophic change.

DR. JOSEPH MULLER, Worcester, Mass.: The oldest lesions are on the neck; they show cigaret-paper–like structure. New lesions at this time are few. A good many of the spots which one sees today appeared two months ago. At that time they were slightly raised. There was no bluish color. They are gradually fading out and regressing to the level of the skin. I performed a biopsy at that time. A histologic study was made, and the slides were presented today. There is no change in the epidermis—no change anywhere except in the collagen fibers, which show decided swelling. No abnormal cells which would suggest a tumor are visible, or at least I could not see any. I think I shall stick to the diagnosis of atrophia cutis idiopathica maculosa.

A Case for Diagnosis (Lupus Erythematosus? Besnier-Boeck-Schauman Disease?). Presented by DR. WILLIAM P. BOARDMAN, Boston.

Two weeks before admission this 15 year old student noticed redness of her hands. Three weeks after that onset destructive lesions appeared on her fingers and an "eruption" on her face. She has had scars on the lower parts of her legs for years. Since onset of the dermatosis there have been a loss of appetite and a loss of 8 pounds (3.6 Kg.) in weight.

On admission there were erythematous infiltrations of the flexor and lateral aspects of the fingers. The extremities were cold. One week later there appeared crusted, keratotic depressed lesions on the fingers at their distal portion, more prominent on the index fingers. All the lesions were pea sized, irregularly circular and pale. There was a pink macular lesion on the left cheek, with fine scaling, about 1.5 cm. in diameter. There were about twelve small papular lesions of the nose and the right cheek, occurring in clusters, and one shallow depressed scar near the right ala nasae. There were several old cyanotic scars on the lower parts of both legs, macular, round and about 3 cm. in diameter.

DISCUSSION

DR. ELLWOOD C. WEISE, Bridgeport, Conn.: I suggest the diagnosis of Hutchison's chilblain lupus, because of the nodular character of the lesions, the central crusting and umbilication and the scars; also the more or less acrocyanotic condition of the hands, all of which go to form the picture of that condition. In lupus erythematosus the individual lesions form patches covering a larger area.

DR. J. H. SWARTZ, Boston: I favor the diagnosis of lupus erythematosus. In simple discoid lupus erythematosus there is decided vasomotor stability of the hernia-like lesions, some of which have definite thrombosis of the vessels, and also the necrotic lesions which are present in this case. This particular patient shows some of these vascular manifestations plus typical lesions of lupus erythematosus on the face. The slide also, I think, is suggestive of lupus erythematosus.

DR. ELLWOOD C. WEISE, Bridgeport, Conn.: The condition can be put to a therapeutic test. It has been rather striking to me to see such conditions respond rapidly to cod liver oil given internally and to local ultraviolet ray therapy. It is my opinion that if this condition is lupus erythematosus response to such simple treatment would not be evident; in fact, such measures might be contraindicated. Keeping the hands and fingers of the patient warm with woolen gloves is desirable.

A Case for Diagnosis (Atopic Dermatitis? Bacterial Dermatitis?). Presented by DR. ARTHUR M. GREENWOOD, Boston.

This 19 year old boy has had eczema since infancy, which has usually been confined to the flexor surfaces. There have been periodic exacerbations and remissions with no relation to habitat, climate or season. Two years ago this condition became progressively worse, spreading for five or six months, until practically the entire body was involved. It has remained more or less unchanged. In youth the patient found by experience that eggs made his condition worse, but in the past few years this type of food has seemed to make no difference. The patient's father has a similar cutaneous disease and was similarly troubled in his youth. A paternal aunt has hay fever. The patient frequently has large open fissures back of the auricles, such as are often associated with bacterial dermatitis.

There is lichenification of the back of the neck and of the antecubital and popliteal fossae, extending from which is a rather uniform scaly erythroderma involving the entire face, the neck, the upper extremities, the upper part of the trunk and the thighs.

DISCUSSION

DR. JOSEPH MULLER, Worcester, Mass.: I looked at the patient and found that there are two types of lesions. One type involves the cubital fossae and the back of the neck. The other type is diffuse inflammation of the face and front of the neck. The appearance of the first type is characteristic of atopic eczema. The long duration of the patient's trouble is consistent with that. The erythematous condition of the face may be of bacterial origin. If it is, I think it is superimposed on atopic eczema, as I am sure that the basic trouble is atopic. The treatment ought to be based on careful cutaneous tests or on the results of elimination diets. For the erythematous lesions I do not know anything better than the usual local applications.

DR. ARTHUR M. GREENWOOD, Boston: This is typical of a number of extremely persistent eruptions for which local treatment is futile as far as my experience is concerned. This young man has had the most expert treatment since the trouble began. He has seen numerous dermatologists, and everything possible has been done. He has lived under the best possible conditions, and nothing has helped him except perhaps temporarily. His eruption is apparently independent of climate, of surroundings and of season. A certain amount of cutaneous testing has been done, with negative results. More complete tests will, however, be made. There is one thing that seems to me possibly to point to a cause for part of his trouble. At various times he has had fissuring of the skin, particularly back of the ears, which in my experience is not associated with uncomplicated dermatitis from external irritants. With the idea that this might be due to bacterial infections I asked Dr. Champ Lyons to see him. He does not feel that the streptococcus is a factor. Dr. Ray has made intradermal tests, and the patient gives a decided

reaction to oidiomycin. It is possible that a yeast is the secondary invader. My theory is that he has a sensitization to external irritants plus an infection with a yeast and possibly with a streptococcus. I hoped some one would have some suggestions as to treatment.

DR. J. H. SWARTZ, Boston: I think there are two notable factors in this case. First, season and climate do not affect the condition, and second, the distribution of the lesions and the history of infantile eczema classify it with what is called at present atopic dermatitis. In this type of involvement, as past experience has shown, although cutaneous tests give positive results, elimination or removal of the so-called allergic agents does not effect an improvement. I fully agree with Dr. Greenwood that there is a bacterial or yeastlike factor, but I think it is secondary.

DR. FRANCIS M. THURMON, Boston: Because of the urticarial phase I should like to make a therapeutic suggestion. Give the patient potassium chloride in 5 grain (0.32 Gm.) doses three times a day for five days.

DR. J. H. SWARTZ, Boston: I have tried potassium chloride in such cases at the Beth Israel Hospital. My experience with the drug has not been as satisfactory as that reported by others who have used it for both urticaria and atopic dermatitis. Perhaps my experience has been too limited to evaluate it.

DR. JOSEPH MULLER, Worcester, Mass.: The fact that the swelling subsided after the injection of epinephrine does not prove its bacterial origin. In urticaria, which is definitely an allergic manifestation, injection of epinephrine produces good results. I think the fact that all the cutaneous tests gave negative results proves nothing, especially as they were performed by an untrained technician. I make all my cutaneous tests myself, and I obtained negative or false positive results on several occasions. If, from the clinical picture, I am positive that I am dealing with a cutaneous allergy, I resort to elimination diets. I clearly remember 1 case in which by doing so I was able to clear up an eruption of many years' duration. Two foods were causing trouble which elicited persistently negative reactions, and three others which elicited positive reactions on repeated examinations proved to be harmless to the patient.

DR. BERNARD APPEL, Boston: I should like to make a suggestion about further diagnostic procedures. I questioned this young man about tests. He said he had had a great many scratch tests but no patch tests. I suggest that he be given contact tests, or patch tests, with some of the substances with which he may come in contact, including flower extracts, perfumes and common materials within his environment. Recently I have made scratch tests on a patient with certain substances and obtained what I interpreted as a negative reaction; subsequently the patient was given patch tests with the same substance, and a positive reaction was obtained. Elimination of that substance resulted in prompt clinical improvement.

I feel that in these types of atopic dermatitis patch tests are as important as scratch tests.

Lichen Nitidus. Presented by DR. C. GUY LANE, Boston.

The patient, a 24 year old white woman, six months before entrance to the hospital, noticed a tan discoloration of the skin on the flexor surface of the wrists. There were no accompanying symptoms. Soon thereafter similar lesions appeared at the elbows, along the arms near the anterior axillary folds and on the skin over the clavicles. She now presents on the flexor surface of both wrists a circumscribed tan area of dermatitis which on closer examination is shown to be made up of individual small glistening papules. The circumscribed area of involvement on the elbows, neck and arms is the color of normal skin and consists of individual yellow-brown papules with shining tops.

Microscopic examination revealed a picture suggestive of lichen nitidus.

Scleroderma (Progressive Type). Presented by DR. J. H. SWARTZ, Boston.

Eight months ago this 28 year old woman noticed stiffness of her fingers, which progressively became worse. Shortly thereafter red macules appeared over the shins and walking became painful. Swelling of the cheeks and eyelids appeared. She noticed that her hands and feet became painful and purple when exposed to cold. The entire process has progressed, making motion difficult.

There is woody edema of the fingers, the dorsa of the hands and wrists, the ankles, the sternocleidomastoid region, the knees, the cheeks, the upper part of the chest and the abdomen. The skin is tense, shiny and thickened, and wrinkles are obliterated. Motion of the fingers, wrists, neck and knees is limited. The hands and feet are cold and cyanotic.

Microscopic examination showed scleroderma.

Under treatment with daily injections of solution of posterior pituitary (double U. S. P. strength) the patient has improved somewhat. A bilateral dorsal sympathectomy has been done.

DISCUSSION

DR. WILLIAM P. BOARDMAN, Boston: The process does not seem to be generalized at present. It may be that treatment has been effective in a short time. In some cases this condition in children clears up spontaneously. I wonder whether the change that has taken place was spontaneous or was due to the therapy.

DR. J. H. SWARTZ, Boston: I prefer to call this condition progressive rather than generalized scleroderma. The changes have been striking as far as changes in cutaneous temperature and consistency of the skin are concerned. The porklike feeling has disappeared to a considerable extent. I have not seen the patient for a long time since the operation, and she has made a decided improvement since the excision was done.

Discoid Lupus Erythematosus with Dissemination. Presented by DR. MAURICE MYER TOLMAN, Boston.

This 23 year old woman had a condition diagnosed in 1936 as discoid lupus erythematosus. She was admitted to the hospital on April 12, 1938, with cervical adenopathy, fever and recurrence of lesions. The white blood cell counts were 2,950 and 4,150 per cubic millimeter. She was discharged and followed in the outpatient department. She was seen again on Nov. 3, 1938, with a flare-up of the old lesions and the appearance of new ones. At that time the white blood cell count was 2,400 per cubic millimeter. She was admitted to the hospital November 25 at which time the white blood cell count was 3,600. Treatment with nicotinic acid was started on November 28. There was a severe vasomotor reaction to 150 mg. three times a day. On December 6 the patient had a chill and her temperature rose to 103.4 F. After five days on 500 mg. daily the white blood cell count was 2,500. She was given five blood transfusions of 500 cc. each and snake venom in a 1 to 3,000 dilution subcutaneously, starting on December 9. Petechiae and bullous lesions developed, and the leukocyte count was as low as 1,900 per cubic millimeter. There was decided improvement after four or five days, and she recovered.

At present there are scattered over her face and neck numerous slightly elevated, reddish macules from 3 to 10 mm. in diameter, which do not fade entirely under pressure and are covered with a grayish to yellowish adherent scale. The entire face and neck appear flushed. The lesions below the eyes and over the nose are confluent.

DISCUSSION

DR. MAURICE MYER TOLMAN, Boston: This case presents several interesting phases. One is the fact that a patient with disseminated lupus erythematosus will recover only if the primary manifestation of the disease has been chronic discoid lesions; recovery does not occur if the onset is acute. Another is the question of hemorrhage in the final stages of the acute disseminated forms of lupus erythema-

tosus, and the third is the question of what role nicotinic acid may have played in the flare-up of this acute condition. This girl showed symptoms of a downhill course prior to the giving of nicotinic acid, manifested by a general feeling of malaise and loss of strength, and there was also a downward tendency of the white blood cell count. When I saw her that day I considered a flare-up probable and sent her into the ward. It was while she was there that nicotinic acid was given. She showed after the first dose a much greater amount of vasomotor flushing than is usually seen, and after the substance had been given for about five days in rather large doses complete dissemination occurred; she was gravely ill and was practically moribund when administration of snake venom was started. I was interested in starting snake venom treatment because I have been interested for some time in seeing patients with this disease while dying bleed and ooze from the gums and other mucous membranes and at autopsy show in the viscera, especially in the stomach, a pool of unclotted blood. Together with the particular type of hemorrhage that one looks for in the extremities, it occurred to my associates and me that this might be some form of ectasia of the minute vessels of the skin. We performed a snake venom test, which at first elicited no reaction. This is consistent with the fact that the chronic discoid lesions do not show reactions to snake venom, whereas the acute ones do. The second test did elicit a reaction; whether it was a coincidence or not, I do not know. Coincidentally with the giving of snake venom in at first minute and then daily larger doses, the girl turned from a practically moribund patient into one who began to feel better; the hemorrhages quieted down; the white cell count, which had gone as low as 1,900 per cubic millimeter, began to go up, and she has been perfectly well ever since. It is only recently, with a slight phalangeal upset, that she has shown any sign of cutaneous lesions. I do not know whether nicotinic acid played any role in the flare-up.

Dr. Francis M. Thurmon, Boston: I should like to say that I have had 2 patients with acute disseminated lupus erythematosus who were gravely ill, and they were treated with snake venom. It is my feeling that is was the snake venom that saved their lives. Both were young girls. The basis for using snake venom was the presence of the hemorrhagic phase of the acute lupus erythematosus, which was proved by the tourniquet test applied above the elbow.

Dr. E. William Abramowitz, New York (by invitation): Of course, hemorrhagic purpura has been reported in cases of disseminated lupus erythematosus. I treated a patient who had had his spleen removed. It may be a passing phase of this disease about which not much is known. Physicians in New York have not had any startling results, so far as I know, with snake venom. It has been used for hemorrhagic purpura mainly. I have been following a different procedure. Up to about two years ago I signed about 5 or 6 death certificates every year of patients who died of acute disseminated lupus erythematosus. I have not signed any since. I started to use sulfanilamide, at first in intensive doses, which I had to discontinue on account of the drop in the platelet count. Since then I have used small doses, 5 grains (0.32 Gm.) three or four times a day. I still take blood counts. I have not encountered any reactions, but at times a patient may have general symptoms of gastric distress and I am obliged to discontinue the drug. In that event I give quinine in the interval and after a time return to the sulfanilamide. I have not done this for the discoid type of condition except in isolated cases in which it has been resistant to gold and bismuth therapy, but I have sent 4 patients with acute disseminated lupus erythematosus out of the hospital and have had others for whom the prognosis was very grave and who have recovered —I do not say they are cured, because it is necessary to watch them for a period of years. The results have, however, been spectacular.

Dr. Maurice Myer Tolman, Boston: As I remember it, this patient was given several transfusions, one prior to the use of snake venom, apparently without any effect on the disease, and one about a day before snake venom treatment was

instituted, and the question was discussed whether the transfusion played any particular part in her recovery. I think it is important to know at which stage of disseminated lupus erythematosus certain forms of therapy are instituted. I think all will agree that the acute type is the manifestation of some toxin probably acting on the blood vessel wall or the minute vessels of the skin. Now if one can attack the toxin before it has done its damage to the vessel wall and if it is streptococcic, sulfanilamide will control it. I think the rationale of snake venom therapy is that the venom counteracts the disease by bolstering up the wall itself. This action is a little different from that observed in treatment of the type of purpura manifested by the tourniquet test, which represents an increase in the pressure of the endothelial system of the wall and the action of nicotinic acid. This is a direct action on the wall by the toxin; if the snake venom has done anything, it has bolstered up the wall itself and has had no effect on the toxin.

FREDERICK S. BURNS, M.D., *President*

BERNARD APPEL, M.D., *Secretary*

Boston, April 12, 1939

Lichenoid Dermatitis? Presented by DR. W. P. BOARDMAN, Boston.

Ten weeks ago this man, aged 39, began to have lesions with itching on the scalp, forehead, trunk and extremities. On the advice of his druggist he used a sulfur ointment without benefit. There is no history of internal medication or dietary change. There now appear pinhead-sized round erythematous papules on the abdomen, buttocks and extremities, especially on the extensor surfaces of the extremities.

The patient's white blood cell count was 5,000 per cubic millimeter, and the red blood cell count, 5,000,000 per cubic millimeter, with hemoglobin 81 per cent, and eosinophils 20 per cent.

Treatment has consisted of the administration of calcium gluconate and propadrine hydrochloride, and starch baths, with no benefit. Enesol caused temporary improvement.

DISCUSSION

DR. J. H. BLAISDELL, Boston: Diagnoses other than lichenoid dermatitis seem possible to me. I suggest, for purposes of discussion, dermatitis herpetiformis or a papular type of urticaria.

DR. F. P. MCCARTHY, Boston: On the patient's first visit I made the diagnosis of toxic dermatitis. The question arises whether one is justified in using this term, as it does not appear in many textbooks as designating an entity, although hospital records indicate its wide use.

DR. J. MULLER, Worcester, Mass.: The interesting feature in the laboratory report was 20 per cent eosinophils, and I think that this rather supports the diagnosis of a papular type of urticaria. If this diagnosis is right, one must think of sensitivity to certain foods. I think some dietary measures might be tried, possibly with good results. The treatment by medicines has not accomplished much.

DR. F. P. MCCARTHY, Boston: May I inquire in what percentage of cases chronic urticaria is due to food sensitivity, as determined by local cutaneous tests for allergy? My impression is that in cases of chronic urticaria of prolonged duration the percentage of positive reactions is very small. I also question whether a dietary restriction in any way would modify the progress of the case.

DR. P. C. BAIRD, Boston: I can answer that question. Allergists state that the results of the tests are negative in 98 per cent of the cases. In the other 2 per cent the reactions are usually so extensively positive as to make interpreta-

tion difficult. In regard to diet, elimination diets have proved to be of considerable service in occasional cases.

DR. J. MULLER, Worcester, Mass.: May I disagree with the preceding speaker? Elimination diets give much better results than cutaneous tests, but I still do not believe that there is a method in medicine which should give 98 per cent false results. I do not claim for the cutaneous tests anywhere near the reliability which some people do, but I do not think that they are wrong 98 times out of 100. I have made a good many tests, and perhaps in one third of my cases I got some information. I shall have to add that in several cases in which I did get a positive reaction the response to the dietary regimen which I instituted on the basis of it proved that the reaction, or my interpretation of the reaction, was false. I fully agree with Dr. Baird that an elimination diet is the way to treat this patient. Cutaneous tests could not be performed at present, since there is insufficient healthy skin left.

DR. E. C. WEISE, Bridgeport, Conn.: I think Dr. Baird was misunderstood. He did not say that 98 per cent of the results of cutaneous tests in patients with this condition were wrong or false. He did say, as I understood him, that 98 per cent of the tests gave negative results. Another point is that I do not see how one could do scratch or intradermal tests on this particular patient because of the severe dermographism which he presents. One can hardly touch his skin without producing a wheal; so intradermal or scratch tests are really out of the question at present.

Lichen Planus Sclerosus et Atrophicus? Dermatitis Lichenoides Chronica Atrophicans (Csillag)? Presented by DR. G. SCHWARTZ, Boston.

This woman, aged 58, was first seen in 1931, at which time she complained of itching in the axillas and around the vulva. The lesions were dry and scaly. In 1932 lesions appeared under the breasts, and a few months later she complained of general pruritus, but there were no new lesions. In 1933 she had a partial vulvectomy for supposed kraurosis vulvae. After this she was treated for a generalized papular rash at the Beth Israel Hospital and later at the Massachusetts General Hospital. She returned to this clinic one month ago.

The patient now shows multiple large diffuse areas arranged symmetrically about the neck, in the axillas, under the breasts, on the abdomen and about the perineum and vagina. She claims that there is intense itching on all parts involved. The lesions are dry, crepe-paper-like, wrinkled atrophic scars, with little thickening. The lesions are sharply outlined and white to silver in color.

DISCUSSION

DR. G. SCHWARTZ, Boston: I think that this condition resembles dermatitis lichenoides chronica atrophicans, as described by Ormsby (Ormsby, O. S.: Diseases of the Skin, ed. 5, Philadelphia, Lea & Febiger, 1939, p. 559). He makes a differential diagnosis between it and lichen planus atrophicus in that there are no black, horny plugs filling in the punctate depressions that one sees first in lichen planus, and he claims that histologically it resembles scleroderma and is believed by many to be an atypical form of scleroderma.

Nodular Myxedema in a Case of Thyrotoxicosis. Presented by DR. J. G. DOWNING, Boston.

On May 10, 1937, this patient, a seaman, reported to the custom house complaining of a dermatitis of the lower thirds of both legs. He was referred to the United States Marine Hospital, where he was treated until July 15, for the dermatitis and also for hyperthyroidism, because his basal metabolic rate was +17 per cent on July 12.

On July 15 the patient was admitted to the United States Marine Hospital with a diagnosis of hyperthyroidism and scleroderma. He was studied from

July 16 until August 3, during which time his basal metabolic rate was found to be +38 per cent. On August 8 he was transferred to the surgical service, and on August 14 a partial thyroidectomy was performed, with removal of practically all the right lobe of the thyroid. The left lobe was not operated on, because of a rise in the pulse rate while he was on the operating table. On September 9 the patient's basal metabolic rate was +4 per cent, and the next day he was transferred to the outpatient department. On November 4 the patient was seen for the first time after discharge to the outpatient department and was found to have a pronounced tremor. He was admitted again on December 13. From Dec. 13 to Jan. 25, 1938, the patient was studied, and during this time his basal metabolic rate was found to range between +55 per cent, on admission, to +21 per cent, just before he was operated on the second time, on January 25. Half of the remaining portion of the right lobe and seven eighths of the intact left lobe were removed. The convalescence was uncomplicated. On March 2 he was transferred to the outpatient department. The condition of his legs was not much affected by either of these hospitalizations and operations. The patient has been kept under outpatient observation from March 17 to the present time. During the greater part of this period he has been taking iodine in some form, such as compound solution of iodine or hydriodic acid. At present he is maintaining a constant weight of approximately 145 pounds (65.8 Kg.) and is not nervous.

Microscopic examination showed a typical picture of localized myxedema of the skin.

DISCUSSION

DR. R. JACOBY, Boston: I should like to suggest lymphangioma circumscriptum.

DR. P. BAIRD, Boston: My impression is that more cases of circumscribed myxedema have been reported from Dr. Stokes's clinic in Philadelphia than perhaps from most of the other places in the world. I should like to suggest that Dr. Anderson, who is a guest of the society today and who was associated with Dr. Stokes for five years, be invited to make a few remarks in reference to this case.

DR. L. E. ANDERSON, Springfield, Mass.: I agree with the diagnosis of circumscribed myxedema in this patient. It is true that Dr. Pillsbury from Stokes's clinic did report a fairly large series of patients with this condition. I personally saw only 2 or 3 of them. The condition of the patients whom I saw was similar to this. The pigskin appearance in this patient, I think, is typical. Circumscribed lymphangioma, I think, can be ruled out definitely. This patient has had none of the semisolid vesicles that are usually in a picture of lymphangioma circumscriptum, and no scarring from former pseudovesicular lesions. The patient certainly appears to be the type in whom one would expect to observe a circumscribed myxedema, because he still has some of the outward signs of hyperthyroidism. He still has some xanthoma. The circumscribed myxedema occurs paradoxically in patients with a basal metabolic rate above normal. In other words, the condition is a localized myxedema in a generalized hyperthyroidism.

DR. E. M. STANDISH, Hartford, Conn.: I think Dr. Anderson explains the situation clearly, because in this particular case the myxedema occurred before the thyroidectomy was performed. If I recall correctly, in Cleveland at the meeting of the American Medical Association four or five years ago, there were 4 or 5 cases in which unilateral myxedema occurred after complete thyroidectomy, and at the time the warning was brought out that a total thyroidectomy should never be performed. Is that so, Dr. Anderson? Does the condition in some cases occur after thyroidectomy or, as in this one, does it always occur before?

DR. L. E. ANDERSON, Springfield, Mass.: I think that in some of the cases the condition occurred after thyroidectomy, but in such cases the thyroidectomy was not complete, and the patient had a recurrence.

DR. J. G. DOWNING, Boston: I think that the largest number of cases was reported by Dr. Paul O'Leary. The case presented is interesting because the condition appeared before there were any operative procedures. There may be 1 or 2 such cases in the literature; in the majority the condition occurs after either partial or complete thyroidectomy. This patient did have some of the translucent vesicles which are described in circumscribed lymphangioma. These were seen to be solid masses of mucin on histologic examination. The interesting and unusual lesions on both legs showed brilliant red areas in the center and a bluish red discoloration at the periphery. At the present time the color has disappeared. There has been definite improvement in both legs. It was noteworthy that this man suffered from intolerable itching and that after the thyroidectomy the itching disappeared.

DR. F. P. MCCARTHY, Boston: The patient states that the condition came on overnight and within a very short time reached the size it now presents. The condition began in the winter, and there is a question of frostbite as the activating factor, which would tend to localize the lesion. The pathologic picture is that of a true mucous edema of the skin, and the sudden onset is extremely interesting, provided the history is correct.

Granuloma Annulare. Presented by DR. E. A. LAFRENIERE, Arlington, Mass.

Several months ago a lesion appeared on the left leg of this Negro child, aged 4 years, and has not changed in appearance since then. The lesion is circular, consisting of a ring about 2 cm. in diameter and nodules about 2 mm. in diameter, on the left leg near the knee.

Physical examination showed coarse rhonchi in the chest. Stereoscopic examination of the chest showed thickening of the right hilus, with areas of peribronchial infiltration extending down from it into the base of the right lung. There is a questionable area of beginning calcification, about ¼ inch (0.6 cm.) in diameter, in the right hilus.

There is a question of childhood tuberculosis and bronchitis. No evidence of pulmonary tuberculosis was found.

DISCUSSION

DR. F. A. CHACE, Fall River, Mass.: I agree with the diagnosis.

Lichen Planus Atrophicus? Morphea? Presented by DR. C. GUY LANE, Boston.

For the past six years this woman, aged 20, has noticed the occasional appearance of small pale spots on the upper part of her back, some of which have slowly enlarged, producing what appears to her to be white scars. Scattered across the upper part of the back are a number of macular and maculopapular lesions varying in color from pale white in the smaller to ivory in the larger ones. The larger patches are slightly raised and present a definite thin red border. Some of the larger patches are kidney shaped. The skin overlying these lesions is atrophic.

DISCUSSION

DR. B. APPEL, Boston: I think that the picture presented by this patient is perhaps a little bit more typical of lichen planus atrophicus than is that in the case presented by Dr. Schwartz, although I am not prepared to differentiate between the two diagnoses proposed for the previous condition. In this particular instance, the lesions are fairly characteristic, showing closely placed follicular plugging, with silvery white, dry, atrophic, sharply outlined areas. In my opinion this case is a fairly classic one of lichen planus atrophicus.

Pseudo Xanthoma Elasticum? Presented by DR. C. GUY LANE, Boston.

About ten years ago this man, aged 26, noticed that the skin on the left side of his neck was becoming a mottled yellow. This process slowly extended around to the right side of the neck. There have been no subjective symptoms. The

patient states that the cervical lymph glands on the left were enlarged previous to the appearance of the neck lesions. The papules do not become pigmented in summer.

Involving most of the left side of the neck and extending around to the right are groups of small shiny yellowish to pink firm papules. Individual lesions measure 1 to 1.5 mm. in diameter and are often grouped in an irregular linear arrangement, averaging 1.5 cm. In places the lesions have coalesced.

DISCUSSION

DR. M. M. TOLMAN, Chelsea, Mass.: I should like to ask if anybody examined this man's eyegrounds. I noticed no mention of it on the record.

DR. C. GUY LANE, Boston: He was examined recently, but I do not know whether there has been any examination of the eyegrounds or not.

DR. J. G. DOWNING, Boston: I suggest the diagnosis lymphangioma circumscriptum.

DR. E. C. WEISE, Bridgeport, Conn.: I agree with the diagnosis as presented, pseudo xanthoma elasticum. The clinical appearance is typical. As to the eyeground findings, I procured an ophthalmoscope and examined the eyegrounds under difficulties. I could not see any angioid streaks; however, that does not mean that they are not there. It would be a good plan to have an ophthalmologist check the fundi.

Erythema Multiforme. Presented by DR. W. P. BOARDMAN, Boston.

About two months ago this woman, aged 28, was bedridden with grip and was taking many pills prescribed by her doctor. She recovered from this, and a pain developed in her chest, which lasted for a week. About one month ago her present eruption developed. She continued taking the pills till about three weeks ago.

She now presents erythematous papules over the dorsa of both elbows, mixed macular purpuric lesions and larger purpuric areas on the buttocks, thighs and legs. There are also many hemorrhagic bullae and vesicles present. There are also several ulcerated lesions.

DISCUSSION

DR. J. H. BLAISDELL, Boston: I should like to inquire if it is possible for a patient to have erythema multiforme for a month with an extensive eruption but without any malaise or recurrent attacks, and also to have it limited to the legs, with none on the backs of the hands, the lower parts of the arms or the mouth.

DR. B. APPEL, Boston: When this patient was seen in the clinic, she had fairly active lesions on the extensor surface of the arms near the elbows, but they have largely subsided. She had no lesions in the mouth.

DR. E. C. WEISE, Bridgeport, Conn.: I should like to make the suggestion that this so-called grip which the patient is stated to have had was no more than the prodromal symptoms or the constitutional symptoms of the impending erythema multiforme. One often finds this in the history; the patient has a little malaise, feels a little "grippy," complains of a sort throat and a short time later has the erythema multiforme eruption. I thought that I saw the remains of old lesions on the extensor surface of the arms near the elbows, and of course active lesions are still present on the buttocks and legs.

Lupus Erythematosus? Presented by DR. M. M. TOLMAN, Chelsea, Mass.

This woman, aged 21, six months ago first noticed on her left cheek one or two small red spots, which developed into "blisters" and increased in size. Gradually new lesions appeared on the right cheek. The appearance and the spread of this condition have always been associated with the presence of vesicles. The condition is asymptomatic except for an occasional mild burning or drying sensation.

Scattered over her face, but generally confined to the medial portions of the cheeks, are eight red round to oval macules, varying from 1 to 4 cm. in diameter. Central paling is present in some, and a questionable atrophy seems to be present in all. At the time of examination all the lesions presented definite small vesicles at the periphery. In some of the lesions an occasional vesicle could be found within the border. There are no lesions in the mouth. Otherwise the results of physical examination are essentially normal.

Cultures from vesicles show Staphylococcus aureus.

Treatment has consisted of weekly intramuscular injections of 2 cc. of bismuth subsalicylate, but the lesions are progressing.

DISCUSSION

DR. M. M. TOLMAN, Chelsea, Mass.: There was a suggestion that the patient might have leprosy. Nasal smears and stains were made, but Hansen bacilli were not found.

Tertiary Syphilodermas. Presented by DR. W. P. BOARDMAN, Boston.

This woman, aged 46, states that about five years ago she had "a few injections" for syphilis. About two years ago she had an eruption which disappeared after a few weeks. Her present eruption began about three and one-half months ago, and new lesions have been appearing continuously. There is some itching.

The eruption is symmetric and consists of nodular dull red grouped lesions, circularly arranged on the face, arms, hands and trunk, with a few lesions on the legs. There is no scarring, and there is slight scaling.

A Hinton test of the blood gave a positive result.

She had one injection of a bismuth preparation one week ago.

DISCUSSION

DR. A. W. CHEEVER, Boston: It is difficult for me to understand the diagnosis of tertiary syphilis. It seems to me that the condition should be classed as a recurring type of secondary syphilis, of which I think it is a reasonably typical example of a rather rare type, the corymbiform. I have observed corymbiform lesions more on the back, it seems to me, than where she has them. I understand that the patient had had just a small amount of treatment, five or six injections, and then had quit. It seems to me that the insufficient treatment would increase the tendency to recurrence.

Lupus Vulgaris? Syphilis? Presented by DR. F. RONCHESE, Providence, R. I.

This man, aged 56, has an annular nodular lesion on the right gluteal region, which has been present about three years. He has had diabetes since 1936.

Microscopic examination showed vegetative dermatitis.

DISCUSSION

DR. J. H. BLAISDELL, Boston: I favor the diagnosis of syphilis for the following reasons: This man presents a chronic destructive condition, and when such a condition is present one should always think of syphilis, tuberculosis and cancer. Obviously the condition is not cancer in this case. Against the diagnosis of lupus vulgaris is the man's age, 56; also the three year duration is a reasonably short time for lupus vulgaris to produce a lesion of this size. The scarring is superficial, and there is little recurrence. There is an area several inches in diameter with only one or two nodules. On the other hand, the condition would seem to be consistent with a diagnosis of a later syphilitic lesion, in spite of the fact, as I recall it, that several tests of the blood gave negative results.

DR. F. P. MCCARTHY, Boston: The histologic section in this case shows the picture of one of the infectious granulomas.

There is an epithelioid cellular reaction in the presence of a few giant cells but no true miliary tubercle formation, and a definite diagnosis differentiating syphilis from tuberculosis cannot be made from the slide.

I favor the diagnosis of syphilis, based particularly on the clinical picture.

Lupus Vulgaris. Presented by DR. B. APPEL, Boston.

Eighteen years ago in this man, aged 43, an eruption developed on the right side of the face several months after there had been a burn in that location. There was a progression of lesions to the left cheek and nose three years ago, and there has been secondary infection for the past few months while he has not had therapy.

At present there are erythematous, scaly, nodular, crusted lesions of butterfly-like appearance on the cheeks, nose, right ear and right upper eyelid. The right side of the face is more extensively involved. The lesions are sharply outlined, and there is a tendency to clearing in the center. Scarring is superficial and not deforming. There are typical apple jelly nodules, particularly on the active borders of the lesions. There is also a bismuth line on both gums.

Microscopic examination in 1935 showed lupus vulgaris.

The patient was treated with ultraviolet rays in 1930, with slight improvement; he had eight injections of a bismuth preparation in 1935; twenty-one injections of gold and sodium thiosulfate in 1935 and in 1936; four injections in 1938, and three injections in 1939.

Lupus Vulgaris (Tumidus). Presented by DR. F. RONCHESE, Providence, R. I.

About seven years ago lesions appeared on the forehead, the right postauricular region and the right popliteal space of this man, aged 24. He lost his right arm in a fireworks accident at the age of 5 years. In June 1937, in an automobile accident, he received a laceration requiring several stitches at about the site of the frontal lesion. The clinical appearance of the lesions was suggestive of naevus comedonicus. Microscopic examination showed lupus vulgaris. Inoculation of guinea pigs with tissue gave a positive reaction for tubercle bacilli.

In 1935 the lesion was desiccated and curetted, with a resulting soft scar, which was visible in the center of the lesion.

He has at the present time a soft, elevated, annular, yellowish red lesion on the frontal and temporal region on the right side, with a scar in the center. On the surface are large openings filled with keratotic plugs. No apple jelly nodules are visible under pressure. Similar lesions are present on the right postauricular and on the right popliteal region.

The reaction to a tuberculin test with a dilution of 1:1,000 was positive. Microscopic examination showed lupus vulgaris.

The desiccation and curettage in 1935 were followed with good results. In February and March of 1939 the patient had roentgen ray therapy, with the result that there was some flattening of the treated areas.

DISCUSSION

DR. B. APPEL, Boston: I should like to suggest that the patient be treated with injections of chaulmoogra oil esters directly into the lesions themselves.

DR. J. G. DOWNING, Boston: I have never seen tuberculosis of the skin that looked like this condition, but I have seen similar conditions due to syphilis. Despite the biopsy and report, I still think that this is syphilis of the skin, and I suggest neoarsphenamine and bismuth for treatment.

DR. J. H. BLAISDELL, Boston: I should think that the recently described treatment, the injection of starch, U. S. P., might well be tried here.

DR. F. P. MCCARTHY, Boston: The pathologic picture in this case is interesting, as the growth is composed of a diffuse epithelioid tissue, with a few giant cells just under the overlying atrophic epidermis. The picture definitely suggests the usual change seen in lupus vulgaris, and since the injections in guinea pigs produced positive results, the diagnosis of lupus vulgaris must be accepted.

SAN FRANCISCO DERMATOLOGICAL SOCIETY

MERLIN TREVOR-ROPER MAYNARD, M.D., *President*

H. V. ALLINGTON, M.D., *Secretary*

April 21, 1939

Pseudopelade. Presented by DR. ERVIN EPSTEIN, Oakland, Calif.

R. M., a white woman aged 32, was referred to me by Dr. Joseph Reis on March 16, 1939. She stated that she had suffered from "eczema" of the scalp for the past twelve years. A small bald spot had appeared on the top of her scalp at the onset. This had not changed particularly until about one year ago, when it started to enlarge.

She now has an irregular palm-sized area of alopecia with atrophy of the scalp. Inflammatory changes are not noted. A few hairs remain in this area, but they can be easily and painlessly extracted. The entire scalp is involved in a dry, scaling eruption which in places is ichthyosiform. There is no history of pustulation. Except for a mild postauricular intertriginous dermatitis there are no lesions of the skin or mucous membranes. The nails are not involved.

Microscopic examination of the hair in warmed 15 per cent solution of potassium hydroxide and culture on Sabouraud's mediums failed to reveal any fungi. Wassermann and Kahn tests of the blood gave negative results.

Therapy to date has consisted of local application of 5 per cent ammoniated mercury ointment plus one subfractional dose of unfiltered roentgen rays.

DISCUSSION

DR. G. V. KULCHAR: I suggest a trial of iontophoresis with acetylbetamethylcholine.

DR. A. E. INGELS: I have seen eruptions that appeared at first to be folliculitis decalvans but later showed features common to pseudopelade. I should like to hear some opinion as to whether one should attempt to differentiate these two conditions or whether they are the same.

DR. HIRAM E. MILLER: I have given up attempting to classify these conditions except to call them cicatrizing alopecia of the scalp. When lupus erythematosus is definitely ruled out, I do not feel that it is possible, or perhaps even therapeutically useful, to classify them further.

DR. J. D. VIECELLI: It is sometimes difficult in a case of cicatrizing alopecia of the scalp to rule out lupus erythematosus.

Tryparsamide Dermatitis. Presented by DR. ERVIN EPSTEIN, Oakland, Calif.

W. L., a white man aged 62, has received eighty-five injections of bismuth subsalicylate, 57 of tryparsamide (each 3 Gm.) and ten fever treatments for tabes dorsalis.

On Feb. 15, 1939 he received the fifth injection in a course of tryparsamide therapy and the same evening he noted pruritus of the dorsa of both hands, the calves, the scalp and the back of the neck. An ill defined eruption appeared in these areas. He was given another intravenous dose of tryparsamide on March 1, which resulted in more severe itching and a more definite eruption. This improved but had not completely subsided when he was given another injection of tryparsamide, one week later. The pruritus and the eruption became more severe.

When first seen by me, on March 10, he presented an erythematous, vesicular, weeping and crusted eruption involving the backs of the hands. On the legs the eruption consisted of an indefinite pruritic area with small erythematous

papules sparsely covering both calves. A number of excoriations were present on the scalp. The back of the neck was involved in an eczematoid eruption with a few excoriated papules.

Tryparsamide was discontinued, and the eruption cleared in about two weeks. On April 14, 3 Gm. of tryparsamide was injected intravenously, with prompt recurrence of the dermatitis. A similar injection was administered on April 19, causing a further exacerbation.

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: The patient stated to me that soap irritates his hands very badly. I suggest that Dr. Epstein try having him rinse his hands in a 1 per cent solution of sodium hexametaphosphate. This substance is said to act as a buffer and to reduce the p_H of soapy water; the calcium and magnesium ions are immobilized by it so that they are unable to form irritating insoluble soaps.

DR. C. J. LUNSFORD, Oakland, Calif.: What are the theoretic limitations of the amount of tryparsamide which may safely be given to patients with syphilis of the central nervous system? I have a patient to whom I have given about one hundred and fifty injections of tryparsamide without any reaction and I remember reading some case reports by Dr. Solomon of Boston who gave patients as much as two hundred to three hundred injections without untoward results.

DR. G. V. KULCHAR: It is not clear to me whether the lesion in the present case appeared in the same place every time.

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: The patient stated that he had a good deal of gaseous distention after every injection. This made me wonder whether the eruption is of gastrointestinal origin and is precipitated by sensitivity to sunlight.

DR. N. N. EPSTEIN: Tryparsamide is tolerated well as a rule, in many cases for long courses of injections. I have recently seen 2 patients who had a serious type of acute reaction. In 1 patient this was fatal. The only tryparsamide eruptions I have seen have followed arsphenamine dermatitis.

DR. ERVIN EPSTEIN, Oakland, Calif.: This patient's eruption recurred in the same location each time, which classes it as a fixed eruption. Cutaneous complications following tryparsamide therapy are rare. According to the cooperative clinical studies, tryparsamide is the least cutaneotoxic of any of the arsphenamines studied (Cole, H. N., and others: Cooperative Clinical Studies in the Treatment of Syphilis; Arsenical Reactions, *Ven. Dis. Inform.* **14**:173 [Aug.] 1933). About the relation of tryparsamide dermatitis to past sensitivity to trivalent arsenicals, 6 of 31 patients showing sensitivity of the skin to the arsphenamines were proved by patch tests to be sensitive to tryparsamide also (Epstein, E.: Sensitivity to Both Trivalent and Pentavalent Arsenicals, ARCH. DERMAT. & SYPH. **36**:964 [Nov.] 1937). Also, I have observed a case of an exfoliative dermatitis and death due to carbarsone, which is chemically closely related to tryparsamide (Epstein, E.: Toxicity of Carbarsone, *J. A. M. A.* **106**:769 [March 7] 1936).

Pemphigus of the Conjunctiva. Presented by DR. HIRAM E. MILLER.

D. N., a white American aged 66, entered the dermatologic clinic on April 18, 1939. His complaints were of a sore mouth and reddened and painful eyes.

A clinical record of two years ago describes pyorrhea accompanied by small white blisters on the oral mucous membrane and thickened eyelids with marked reddening and definite scarring of the conjunctivas.

Recent examination of the mouth disclosed bullous lesions varying from 5 to 20 mm. in diameter, surrounded by a circumscribed red border. These lesions were scattered along the gingival margins and the buccal mucosa and extended into the laryngeal portion of the pharynx; the epiglottis and the soft tissues were involved. The nose was free of lesions. The eyelids were injected and scarred,

and small vesicles were seen near the limbus of the right eye. There were no cutaneous manifestations except one bullous lesion on the penis, near the sulcus. The observations at physical examination were otherwise noncontributory.

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: We are privileged in being able to observe this case of ocular pemphigus because of the rarity of the condition. It is called "essential shrinkage of the conjunctiva" by the ophthalmologists.

DR. HIRAM E. MILLER: I was somewhat surprised to see a positive diagnosis of pemphigus at the head of this case history. It was a tentative diagnosis only. Dr. Templeton's reference to essential shrinkage of the conjunctiva is of interest. This patient had been in the clinic for patients with ocular diseases two years previously, and that was the actual diagnosis made at that time.

Pseudoatrophoderma Colli(?). Presented by DR. C. E. SCHOFF, Sacramento, Calif.

J. S. P., a white housewife aged 50, has had an eruption on her neck for eighteen or nineteen years. It began symmetrically on the anterolateral surface of the neck without apparent cause and has spread slowly.

At present the involved area shows a retiform pigmentary change which includes the lateral and the anterior surface of the neck to a point 1 inch (2.5 cm.) below the suprasternal notch. On close inspection it is noted that there are areas varying from 0.2 to 0.5 cm. in diameter which are depigmented and apparently lighter than the normal surrounding (brunette) skin. These areas have the appearance of being atrophic. Surrounding these are hyperpigmented folds of skin. There are no subjective symptoms associated with this change, nor have there ever been. As a girl the patient used to work in the fields. She has spent most of her life in the Sacramento Valley and the San Francisco Bay region.

She has four children alive and well. One child died at the age of 3 months from intestinal trouble. One daughter, also presented tonight, has a similar pigmentary disturbance. No history of involvement of other members of the family could be obtained. A laparotomy was performed three years ago for "tumors of the womb." Since that time the patient has not menstruated.

No change has been noted in the skin which could be attributed to the operation. There has never been any apparent relation between the cutaneous changes and the menstrual cycle.

Kolmer, Kline and Kahn tests gave negative results.

A blood count was normal.

Urinalysis showed a faint trace of albumin, and 8 to 10 finely granular casts, 5 to 7 leukocytes and 2 to 3 erythrocytes per high power dry field.

Pseudoatrophoderma Colli(?). Presented by DR. C. E. SCHOFF, Sacramento, Calif.

D. S., a white woman aged 30, a daughter of the patient just presented, demonstrates a similar anomaly of pigmentation, affecting the anterior lateral surfaces of the neck and the upper anterior part of the chest. This began insidiously in the suprasternal notch three or four years ago.

The changes in the skin occupy the areas of the base of the neck and the exposed surfaces of the upper part of the chest. The skin appears folded in very fine cross rugae. These folds show an increased brownish pigmentation, and the intervals between them appear depigmented, shiny and atrophic. The skin is flexible, and the folds flatten on stretching.

This is the same general picture as is presented by the mother, but it is less marked in all respects except the atrophy. There are no subjective symptoms. There have been no serious illnesses. There was questionable pulmonary tuberculosis at about the twelfth or thirteenth year. At that time there was also a

cessation of the menses for four months, and she was told it was due to the condition of her lungs. She recovered rapidly and has had no further clinical signs of pulmonary involvement.

Kolmer, Kline and Kahn tests gave negative results. The blood count and the urine were normal.

DISCUSSION OF CASES OF PSEUDOATROPHODERMA COLLI

DR. A. E. INGELS: In the differential diagnosis it might be well to think of acanthosis nigricans.

DR. H. J. TEMPLETON, Oakland, Calif.: I wish to differ from the diagnosis, basing my opinion on my experience with 1 patient. Some time ago, shortly after Becker published his description, I presented before this society a patient with a condition that I labeled pseudoatrophoderma colli. Recently Dr. Becker saw her with me and agreed with the diagnosis. However, her condition does not look anything like that of this patient. Her lesions are depigmented and flat and vary from a few millimeters to 1 cm. in diameter. They have a sheen and a crinkly appearance.

DR. ERVIN EPSTEIN, Oakland, Calif.: The patients studied by Becker and Muir (Becker, S. W., and Muir, K. B.: Pseudoatrophoderma Colli, ARCH. DERMAT. & SYPH. **29**:55 [Jan.] 1934) and by Frost and me (paper to be read at the 1939 meeting of the American Dermatological Association) were young women. The lesions apparently clear spontaneously at some time. No cases have been reported in which the patients were elderly persons. After bathing the lesions are usually clearer because the parakeratotic scale is removed. It is this scale rather than true pigmentation that causes the color. The lesions tend to follow the lines of cleavage of the skin. As they clear, they leave a whitish area which resembles atrophic skin. The darkened skin is thrown up into tiny folds.

DR. J. M. GRAVES: I think it would be wise to perform a biopsy and look for elastic tissue. I think it is possible that this is pseudoxanthoma elasticum.

DR. H. V. ALLINGTON, Oakland, Calif.: I was likewise about to suggest the diagnosis of pseudoxanthoma elasticum.

DR. HIRAM E. MILLER: From this one examination, I am inclined to agree with the diagnosis of pseudoatrophoderma colli. There is a rather diffuse hyperpigmentation with some depigmentation, and the epidermis is thrown up into folds. The diagnosis of pseudoxanthoma elasticum must be considered. The yellowish, discrete, pinhead-sized to pea-sized papules seen in that disease are not present in this patient, however. Pseudoxanthoma elasticum does have a tendency to occur in more than one member of a family, as is observed in these 2 patients. As far as I know, a familial tendency of pseudoatrophoderma colli has not been reported. Examination of the eyegrounds to determine the presence or absence of angioid streaks would be of value.

Arsenical Pigmentation and Keratoses. Presented by DR. HIRAM E. MILLER.

A. J., an American-born Chinese man aged 22, entered the University of California medical clinic complaining of periodic attacks of asthma since the age of 5 years. He has had no previous medical consultation and has relied on Chinese herbs and pills for relief. During the past two years he has noticed that his skin was becoming darker and that calluses were developing on his palms and soles.

There is diffuse pigmentation of the skin, most pronounced on the trunk. This pigmentation is mottled and grayish. The skin is dry and warm, but there is no scaling. There are numerous punctate hyperkeratotic areas on the palms and soles.

Physical examination otherwise gives essentially negative results. Roentgenograms of the chest were normal. Roentgenograms of the paranasal sinuses showed slight cloudiness of the antrums and the ethmoid cells.

Chemical analysis of the urine did not reveal arsenic. Chemical analysis of the hair has not yet been reported on.

DISCUSSION

DR. FRANCES TORREY: I felt that if this were a case of arsenical pigmentation one ought to be able to find some evidence of arsenic in the urine or in the hair. Up to the present time this has not been found. If the patient had continued to ingest arsenic in pills over a long period until recently, there should be some laboratory evidence of it.

DR. H. J. TEMPLETON, Oakland, Calif.: This is as classic a picture of arsenical pigmentation and keratoses as one could find. If this is not arsenical dermatitis, the whole idea of the picture must be revised.

DR. G. V. KULCHAR: Why not give a test dose of sodium thiosulfate?

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: Is it not true that when patients are no longer taking arsenic, the arsenic cannot be demonstrated in the urine except when sodium thiosulfate is given? I noted that this patient does not have greenish hair.

DR. ERNEST K. STRATTON: I suggest microchemical analysis of a biopsy specimen of this patient's skin. The department of pharmacology of the University of California is equipped with apparatus and reagents which show the characteristic crystal formation if arsenic is present.

DR. ERVIN EPSTEIN, Oakland, Calif.: One might stain for arsenic in the tissues by the method of Osborne (Osborne, E. D.: Microchemical Studies of Arsenic in Arsenical Dermatitis, ARCH. DERMAT. & SYPH. **18**:37 [July] 1928).

DR. HIRAM E. MILLER: This is a classic picture of arsenical pigmentation and keratoses. If chemical tests fail to reveal the presence of arsenic, there is something wrong with the tests.

Hydroa Aestivale. Presented by DR. H. J. TEMPLETON, Oakland, Calif.

F. R. H., a white man aged 43, states that during the last two summers he has noticed pruritic papules wherever the sun strikes his skin. The eruption appears in the spring, persists throughout the summer and disappears during the fall. It is limited to the face, ears, neck and hands. He states that it appears on his trunk if he takes a sun bath. His brother is said to have the same disease. There is no history of reddened urine.

Morphologically the lesions are fairly superficial but perceptibly indurated papules measuring 2 to 5 mm. in diameter. A few are capped with vesicles, and some are crusted.

No laboratory work has been done yet.

The patient was instructed to protect one hand with a 4 per cent menthyl salicylate lotion and then to expose both to sunlight experimentally.

DISCUSSION

DR. N. N. EPSTEIN: I agree with the suggestion that this is an actinic dermatitis but lacks some of the characteristics of hydroa.

DR. H. J. TEMPLETON, Oakland, Calif.: This patient does not show the degree of activity in the lesions that was shown a week ago, probably because he has improved during the recent foggy weather. It seems to me that from a truly scientific standpoint one should refer to his condition as "light sensitivity," to describe the disease from the standpoint of etiology. On the other hand, I do not think one should abandon the old morphologic classification. These lesions are firm, shotty papules; so I think the old term "hydroa aestivale" is a good one.

Atrophic Process of Glans Penis with Epithelioma. Presented by DR. H. J. TEMPLETON, Oakland, Calif.

R. W. G., a white man aged 54, consulted me on Jan. 16, 1939, because of a dime-sized ulceration of the glans penis which had been present for one and a

half years. There was no regional adenopathy. A biopsy showed grade 3 squamous cell epithelioma. The lesion was radically destroyed by electrodesiccation, and healing occurred in three months.

The mucous membrane of the glans penis, aside from the scarred area, shows a peculiar mottling of whitened and reddened areas. The patient stated that the aforementioned epithelioma began in a similar mottled and reddened area.

Although the diagnoses of leukoplakia, lichen planus and erythroplasia of Queyrat were considered, I feel that the condition belonged more in the group of atrophies, such as balanitis xerotica (analogous to kraurosis vulvae in the female).

DISCUSSION

DR. G. V. KULCHAR: I agree with the diagnosis of balanitis xerotica obliterans.

DR. N. N. EPSTEIN: I agree with that diagnosis.

DR. HIRAM E. MIILLER: It has been our experience in cooperation with the genitourinary staff that local removal of an epithelioma of the glans does not cure the condition. It generally is wise to remove most or all of the organ.

DR. J. M. GRAVES: Don't you think another epithelioma is developing now? There is one crusted lesion.

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: I do not think one can rule out atrophic lichen planus without a biopsy.

DR. H. J. TEMPLETON, Oakland, Calif.: This man is young and virile. He objected to our removing any more of the penis than was necessary.

Syringomyelia (Lumbosacral Type). Presented by DR. JOHN M. GRAVES.

M. H., a white American woman aged 23, presents a deformity of the left foot, diminished cutaneous sensation of the left leg and difficulty in walking. On March 13, 1939, there were widening and distortion of the left toes, absence of the fourth toe and absence of all nails. There were bluish discoloration of the skin and a brawny induration of the subcutaneous tissue of the leg and foot. Diminution to absence of pain and temperature sensation was demonstrated to the level of the hip joint. The peroneal group of muscles were atrophic. Neither ankle nor knee jerks were elicited.

The present condition began at the age of 8 as painless ulcerations of the four toes. These healed within a year, but the sense of touch was diminished in the foot. There have been repeated exacerbations of the ulcers, increasing deformity of the foot, progressive difficulty in walking and spreading of the anesthesia.

Sections of a biopsy specimen taken Aug. 1, 1930, showed atrophic changes; there was no evidence of leprosy.

DISCUSSION

DR. HIRAM E. MILLER: We considered the diagnosis of leprosy or syringomyelia in this case. Since a positive diagnosis of leprosy could not be made, we concluded, more by elimination than anything else, that the condition is syringomyelia.

Malignant Melanoma. Presented by DR. NORMAN N. EPSTEIN.

J. B., a white man aged 61, first noticed a small nodule on the vertex of the scalp about three months ago. This has increased in size. Examination revealed a bean-sized bluish black nodule in the scalp, surrounded uniformly for a distance of about 1.5 cm. by a deposit of coal black pigment.

A small lymph node located posteriorly on the right side of the neck showed metastatic malignant melanoma on pathologic examination. There was no evidence of metastasis elsewhere.

Roentgen ray treatment has been given.

DISCUSSION

DR. G. V. KULCHAR: How about application of roentgen rays to the pituitary gland?

DR. L. R. TAUSSIG: I was interested in the fact that the radiologists are now willing to treat melanomas. For years they did not want to do so. Recently some of them have become enthusiastic about giving cauterizing doses of roentgen rays for melanoma.

DR. H. V. ALLINGTON, Oakland, Calif.: Did the patient have any lesion there previously?

DR. N. N. EPSTEIN: No; there was no history of any.

A Case for Diagnosis (Pemphigus? Epidermolysis Bullosa?). Presented by DR. N. N. EPSTEIN.

M. McM., a white man aged 55, had bullae on the hands, scalp and face first in 1936. These became secondarily infected, and persistent pyoderma developed. The patient was never free of lesions, although the condition varied in severity. At one time bullae appeared on the forearms and lower limbs. Many of the lesions have been associated with trauma.

The patient has been a morphine addict and chronically alcoholic.

Various treatments, including injections of coagulen and sulfanilamide, have been given.

Routine laboratory work revealed nothing contributory.

DISCUSSION

DR. CHARLES ALBERT SHUMATE: This patient was first seen by me several years ago. He had at that time what I believed to be impetiginized lesions. Later bullae developed on his body and in his mouth. The impression at that time was that he had pemphigus. Last fall he claimed that trauma preceded the appearance of each lesion. A diagnosis of epidermolysis bullosa was then considered.

DR. N. N. EPSTEIN: This man has had an interesting history. At one time, about a year ago, he had clear bullae which developed without relation to trauma. The condition was thought to be pemphigus. I think, however, that that diagnosis is open to question, because now some trauma appears to be necessary for the appearance of the lesions.

Epidermolysis Bullosa Congenita. Presented by DR. H. J. TEMPLETON, Oakland, Calif.

B., a white girl aged 3 days, was referred to us by the physician who delivered her, Dr. F. L. Herrick, of Livermore, Calif., because of stripping off of the skin of the hands, feet, lips and trunk.

Dr. Herrick stated that when he cleansed the infant's mouth at birth the skin around the lips peeled off. Later it was noted that the skin peeled off of the hands, feet, buttocks and trunk at sites of trauma.

A paternal uncle died at birth of a similar disease which was diagnosed as pemphigus neonatorum. Both parents recently had negative Wassermann reactions.

The diagnosis of bullous syphiloderm was considered but was ruled out on the basis of negative Wassermann reactions of the parents and negative results from dark field examinations of the baby.

Bullous impetigo neonatorum was ruled out because of the existence of the lesions at birth and because of negative smears and cultures of fluid from unruptured blebs.

The diagnoses of epidermolysis bullosa and pemphigus neonatorum have been suggested.

The baby is being treated by tanning the eroded areas with Burwick's dye (brilliant green 1 per cent and crystal violet 1 per cent in 50 per cent alcohol).

She is tube fed, and generous amounts of vitamins are given. Feedings are well tolerated. Although her general strength is better and the older lesions are improving, new areas of skin are still stripping off. The child is now 17 days old.

DISCUSSION

DR. ERVIN EPSTEIN, Oakland, Calif.: I suggest the use of moccasin snake venom in this case. I used it in 1 case of epidermolysis bullosa. Afterward the bullae were much more difficult to elicit. One can use it in the form of a 1:3,000 solution, starting out with 0.1 cc. hypodermically and building up the dose according to the patients's tolerance.

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: I have followed a family in which the mother, a daughter and a son all had severe epidermolysis bullosa. Anterior pituitary extract was given until both the girl and the boy had hypertrophy of the breasts. No benefit was received.

DR. ERNEST K. STRATTON: I should like to have Dr. Templeton try rabies vaccine in this case. In view of the work done by Grace in isolating a virus from subjects with pemphigus, it is not unlikely that a virus is responsible for epidermolysis bullosa also. Experimenters have found that rabbits infected with the virus of rabies cannot be inoculated with the virus of pemphigus and vice versa.

Argyria. Presented by DR. N. N. EPSTEIN.

J. B., a white man aged 65, was first seen because of an ashen gray color of the skin of the face, neck and upper portion of the trunk in October 1938. The scleras also were involved.

The patient states that he has used neo-silvol nose drops daily for several years.

On microscopic study, sections from a biopsy specimen taken from the neck on October 19 appeared normal except for a few subepidermoid perivascular collections of lymphocytes, mononuclear phagocytes and a few eosinophils. In some of these areas the phagocytes contained finely divided black pigment. A few of the vessels were engorged. The pigment largely disappeared after treatment with iodine followed by sodium thiosulfate.

DISCUSSION

DR. G. V. KULCHAR: I saw this man after he had used the neo-silvol nose drops only four or five months. He had generalized argyria at that time.

DR. A. E. INGELS: The sections examined with the dark field microscope according to the method described by Eric Hoffmann are striking. Sections stained with Giemsa's stain show the silver deposited densely in a "line" parallel to the basal layer and outlining the hair follicles and the acini of the sweat glands. I examined sections from this man some time ago, when he was a patient at the Laguna Honda Home.

DR. N. N. EPSTEIN: It is interesting in this case that the argyria is most marked on the upper part of the body, close to where the silver was applied.

A Case for Diagnosis (Tuberculous Granuloma of the Nose?). Presented by DR. FRANCES TORREY.

J. B., an American boy aged 13, entered the University of California dermatologic clinic complaining of swelling of the nose and difficulty in breathing for the past month.

Excision of tuberculous cervical glands had been done at the age of 1 year and again at the age of 2 years. At the age of 5 years the patient had tuberculosis of the thoracic portion of the spine and was treated at the Shriner's Hospital. At the age of 8 years he had lacrimation of the right eye with a subsequent purulent discharge. This did not respond to the passage of sounds and irrigations. About one year ago he had a series of small pustules (?) on the upper lip and

subsequently "sores" inside the right nostril, which responded to treatment with ointments. One month ago the tip of his nose began to swell; it became reddened and sore.

Examination shows excessive lacrimation of the right eye, with a purulent discharge that may be expressed from the enlarged lower punctum. There is decided redness of the tip of the nose, especially on the right side. This area is indurated but not tender. The right nasal passage is almost occluded by granulation tissue. The remainder of the physical examination gave essentially negative results. Roentgenograms of the chest showed no conclusive evidence of pulmonary parenchymal infiltration, although the hilar shadows were increased. The Wassermann and Kahn reactions were negative. The sedimentation time was within normal limits.

A biopsy was done a week ago. A guinea pig was inoculated with half the tissue, and the rest was prepared for microscopic study. No acid-fast organisms were found on direct examination of the material.

DISCUSSION

There was no discussion of this case.

Lupus Erythematosus. Presented by DR. A. E. INGELS.

C. L., a white woman aged 39, a telegraph operator, came to my office on Dec. 16, 1938.

She had always been well until last summer during her vacation, when she sustained a severe sunburn after walking outdoors without a hat all day, in contrast to her previous indoor city life. She states that ever since this time she has not felt well and has had no "pep." The initial severe sunburn cleared, but the nose continued to peel. A fiery red plaque developed on the tip of the nose about the first of November. In a short time it started to weep. The lips and the gums were extremely sore at this time. A superficial ulcer developed on the lower lip and shortly spread over the entire lip. The mouth was treated with gargles during this time, but the gums became more sore and tender.

There were no abnormal physical findings except in the skin. When first seen the nasal lesion consisted of a crusted, highly inflamed and weeping plaque 3 cm. in diameter, occupying the tip of the nose. The horny crust could be lifted up with ease, the under surface then showing a dense studding of horny plugs, leaving patent follicles. The lips showed redness, swelling, crusting and superficial ulceration. The mouth had a fetid odor (no bismuth had been given), and swelling and soreness of the gums were seen.

Repeated dark field examinations for Spirochaeta pallida have all given negative results. Two Wassermann tests, one performed about the middle of December and one the first of April, gave negative reactions. Two examinations for Coccidioides immitis gave negative results. Roentgenograms of the teeth showed no abscesses or devitalized teeth. Roentgenograms of the sinuses were clear. The urine was normal.

Examination of sections showed the epidermis to be normal except for slight intercellular and intracellular edema. The cutis showed rather heavy round cell infiltration, which was centered mainly around the follicles and sweat glands and about the vessels. Both polymorphonuclear leukocytes and lymphocytes were seen. No giant cells, epithelial cells or tubercle formations were present. Dilated sweat glands were observed. Van Gieson and elastic tissue stains showed homogenization, i. e., formation of elastin and colasin. A section stained with Becker's stain showed absence of pigment in the basal cell layer. Horny plugging in some of the hair follicles was seen.

Weekly intramuscular injections of bismuth subsalicylate and iodobismitol and a ketogenic diet have been given. Plasmochin, ⅙ grain (0.01 Gm.) twice daily, has also been given. The patient feels much better. The lesions have improved considerably.

DISCUSSION

DR. N. N. EPSTEIN: In addition to lupus erythematosus, I think one of the bullous diseases must be considered. The course of the condition will tell the story.

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: Is there any history of ingestion of drugs?

DR. A. E. INGELS: There is no history of intake of drugs. I feel that at present lupus erythematosus is the most tenable diagnosis. In addition to the histologic picture, which is consistent with this diagnosis, the clinical behavior of the lesion on the nose seems important.

Purpura Annularis Telangiectodes. Presented by DR. H. J. TEMPLETON, Oakland, Calif.

H. G. B., a white man aged 42, consulted me on March 24, 1939, because of coin-sized purpuric rings located on the buttocks and thighs. These have been present for about five years.

The patient states that the lesions begin as pea-sized pinkish macules which gradually enlarge, clearing in the center to form rings.

Inspection reveals a few pea-sized macules and many coin-sized purpuric rings. The centers of the ringed lesions show some evidence of atrophy.

A blood count showed a hemoglobin content of 80 per cent. There were 4,600,000 erythrocytes and 6,850 leukocytes per cubic millimeter. A differential count showed 70 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes and 6 per cent mononuclear leukocytes. There were 320,000 blood platelets.

Histologically there were no noteworthy changes in the epidermis. In the pars subpapillaris there was a sharply demarcated cellular infiltrate consisting mostly of lymphocytes. Vascular changes were minimal, and there was no free hemorrhage.

DISCUSSION

DR. L. R. TAUSSIG: I agree with the diagnosis. I think this is a typical case of Majocchi's disease. I do not believe that there is a specific histologic picture in this condition.

DR. EUGEN OSTWALD (by invitation): My associates and I treated some such conditions in Europe by destroying the lesions most annoying to the patient with desiccation, but I should like to know whether Dr. Templeton or any of the members has any other suggestion.

DR. A. E. INGELS: Clinically, I agree with the diagnosis. However, I feel that further microscopic study of the sections is needed.

DR. HIRAM E. MILLER: This might be another case in which to try snake venom.

DR. H. J. TEMPLETON, Oakland, Calif.: This patient has no subjective complaints; so I do not think one would be justified in using destructive therapy. I think instead that the condition should be attacked systemically if treated at all—say with vitamin C.

Localized Atrophy of Skin and Subcutaneous Tissue (Hemiatrophia Faciei? Scleroderma?). Presented by DR. H. V. ALLINGTON, Oakland, Calif.

A. S., a white housewife aged 31, is presented from the Berkeley General Hospital Dermatologic Clinic. She was referred to me by Dr. Wallace Partch because of areas of atrophy of the skin and subcutaneous tissue. The largest one involves the left side of the forehead. It extends from the supraorbital ridge as a band 4 or 5 cm. wide into the left frontal portion of the scalp. Irregular areas continue over the left side near the midline to the occiput. Another, 2 to 3 cm. in diameter, is present just below and to the right of the external occipital protuberance. Other lesions, from 5 to 8 cm. in diameter, are present to the left of

the spine of the first dorsal vertebra, over the medial aspect of the left foot and on the lateral surface of the right foot. The lesion on the left side of the forehead and scalp began at the age of 16. The others are relatively inconspicuous, and the date of their onset is not known. The lesions are thought to be slowly increasing in size. The patient remembers no redness, swelling, hardening or pain in the involved areas either before or since the onset. At present there is no notable change in the color of the skin. The atrophy involves both the skin and the subcutaneous tissue. In the scalp the more advanced lesions are shiny and smooth and the hair is absent. There is no palpable infiltration of the margins of the lesions except possibly in the medial margin of the lesion on the forehead, and there it is slight. The areas are slightly hypesthetic, but Dr. Lester Lawrence, who made a neurologic examination, feels that this is due to local atrophy of the sensory apparatus rather than to any disturbance of the regional or central nervous system.

In addition to her cutaneous troubles, the patient has complained of nervousness, constipation, nausea, heartburn, premenstrual pain and hot flashes. Salpingectomy was performed on each side, and oophorectomy on the left side in 1932. There is general dryness of the skin. Pelvic examination by Dr. Harry Aitken revealed a tender mass in the right adnexal region, probably a cystic right ovary.

The basal metabolic rate on Aug. 23, 1938 was —16 per cent. A Kline test on August 20 gave a negative reaction. The sedimentation time on October 17 was three hours (Linzenmeier method).

Roentgenograms of the skull were described by Dr. L. M. Knox as follows:

"There is no evidence of atrophy of the outer table of the skull along the left frontal region. There is nothing to indicate any difference between the left half of the cranium and the right half. However, the areas on the two sides of the midsagittal plane in the parietal regions show a filmy light decalcification in which the normal trabeculation of the bone is absent. This sort of change one sees with Paget's disease of the bone."

Administration of 1 grain (0.06 Gm.) of thyroid daily and injection of gonadotropic substance from the urine of pregnant women have resulted in some improvement of the patient's general condition.

DISCUSSION

DR. J. M. GRAVES: It was almost impossible for me to believe that there was nothing wrong with this woman's skull. The condition seemed to me to be the end result of scleroderma.

DR. C. E. SCHOFF, Sacramento, Calif.: I have a similar case, the patient being a girl whose involvement extends well up into the parietal region. At times the objective symptoms manifest themselves as numerous nodules which appear to be situated in the subcutaneous tissue. The entire area involved extends from the angle of the jaw to the outer margin of the orbit and "fans out" over the temporal, the parietal and the posterior frontal region. When I first saw her, a number of years ago, I made a clinical diagnosis of sarcoid. Subsequently I changed the diagnosis to scleroderma, and more recently I have felt that the proper diagnosis would be hemiatrophia faciei. A point of interest is that during the so-called active stages, when she has been treated with gold sodium thiosulfate, the inflammatory reactions and the nodules disappear.

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: This patient has muscular atrophy. I wonder whether it may be of neurologic origin and a form of hemiatrophy.

DR. HIRAM E. MILLER: I think that this is the usual type of involvement seen in scleroderma of the "en coup de sabre" type.

DR. H. V. ALLINGTON, Oakland, Calif.: A diagnosis of hemiatrophy was considered the most tenable one until it was found that the lesions occurred on both sides of the body.

A Case for Diagnosis (Thickening and Exfoliation of Mucous Membrane of Mouth). Presented by DR. H. V. ALLINGTON, Oakland, Calif.

A. M., a white man aged 22, presents areas of milky white ragged, sodden, exfoliating oral mucous membrane. The process is maximal on the cheeks, opposite the premolar and molar teeth, but occurs also in places on the lingual, gingival and labial surfaces. It began four or five years ago. It causes no discomfort.

The patient is conscious of biting his cheeks frequently. Whether this habit is the result of the mucosal changes or whether it is a factor in causing them is questionable.

The patient's father is said to have similar lesions in his mouth, which have been present for many years. The patient's general health is good. There are no associated cutaneous lesions. There are numerous amalgam fillings in his teeth. Reactions to patch tests on the skin of the forearm with amalgam and with a 1 per cent ammoniated mercury ointment were absent at forty-eight hours, but strongly positive delayed eczematous reactions developed a week later to both.

A Kline test gave a negative result. A blood count was normal. Microscopic examination and cultural examination failed to reveal yeasts.

The diagnoses considered included intolerance to the mercury in amalgam fillings and hereditary hyperkeratosis and exfoliation of the mucosa.

DISCUSSION

DR. N. N. EPSTEIN: I thought the lesions could not be distinguished from those of leukoplakia or possibly lichen planus.

DR. C. J. LUNSFORD, Oakland, Calif.: I saw the patient in the office and thought the condition was most probably lichen planus. Clinical differentiation, however, is very difficult. I did not know that patch tests had been subsequently made.

DR. H. J. TEMPLETON, Oakland, Calif.: I should have the amalgam fillings taken out of this man's mouth.

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: I thought of dentifrices, and also that he might have been chewing the area. I have seen a patient with an eruption of the palm and soreness of the mouth after using a proprietary tooth paste (Dr. Strasska's). Also, the habit of biting a small excrescence in the mouth might be a factor. Sodium perborate if it is used, will cause whitened areas in the mouth. I think these conditions might be considered rather than leukoplakia.

DR. HIRAM E. MILLER: The more severe areas on the inner surfaces of the cheeks are directly opposite the amalgam fillings. The lesions have been present for five years and the fillings for six years. If the patient were under my care, I should advise that the fillings be removed.

DR. C. E. SCHOFF, Sacramento, Calif.: In the patients that I have observed with pseudomembranes due to electrolytic phenomena as described by Lane there has been direct contact between the fillings and the tissue on which the membranes have formed. In this patient I did not see any fillings that were in direct contact with the involved area.

DR. H. V. ALLINGTON, Oakland, Calif.: I think this patient's condition is different from ordinary leukoplakia. If a dull curet is run over the area, large chunks can be easily peeled off, and the mucosa beneath is dull red and ragged. The lesion is sheetlike rather than reticular, as in lichen planus.

I have asked the patient to have all the fillings removed and replaced by gold, but he has objected on the grounds of expense.

Urticaria from Cold. Presented by DR. H. V. ALLINGTON, Oakland, Calif.

W. W. W., a white University of California student aged 22, has had localized areas of edema following exposure to cold for the past ten years. He associates the onset of this with being struck by a sting ray while surf bathing. This history is indefinite, however.

The intensity of the reaction gradually diminished until two years ago, when it flared up after a severe attack of poison oak dermatitis. At present, exposing

any part of skin to cold results within two or three minutes in a tense swelling limited to the area exposed. There is little change in color, the area being, if anything, paler than normal. Both subjectively and objectively the area feels tense and cold. The reaction begins to disappear in about thirty minutes. There is no general disturbance. For example, swelling of the hands occurs if they are exposed to the wind while riding to school. A cold shower will cause widespread giant urticarial swelling over the trunk and extremities, while a lukewarm or hot one will not. There is no increase in reaction to mechanical stimulation (dermographia), and the skin appears to respond normally to light.

The patient has had no serious illnesses. A weakly positive tuberculin reaction was observed in 1936. Roentgenograms of the chest were normal at that time. On April 11, 1939 the urine was normal and the Kline reaction was negative.

DISCUSSION

DR. ERNEST K. STRATTON: The patient states that the attacks of urticaria brought on by exposure to cold date from the time he was wounded by a cold water fish. Perhaps he could be desensitized by injecting small doses of an extract made from this animal.

A Case for Diagnosis. Presented by DR. CHARLES ALBERT SHUMATE.

N. O., a Japanese ranch laborer aged 52, a resident of Yuba County for the past thirty years, was seen by Dr. H. E. Alderson as a private patient.

He presented several dark red, round, slightly elevated nodules 1 cm. in diameter on his neck and left eyebrow and also a series on his left arm. Smaller ones were found on his right arm and trunk. The first nodule appeared on his neck about March 10, 1939.

At Yuba City a local physician gave him sulfanilamide for seven days. He stopped work but was exposed to sun. On about April 3, macular erythematous areas appeared profusely on the hands, face, legs and back. Since the drug was discontinued the erythema has gradually faded.

At present treatment consists of giving sodium salicylate tablets, one every four hours, and the condition has improved without any other treatment.

The patient was healthy and strong up to fourteen years ago, when he first noticed slight atrophy of the left arm. This slowly increased until seven years ago, when he was seen by Dr. Howard Naffziger, who advised removal of abscessed teeth and gave the patient drops to take internally. Dr. Naffziger's diagnosis was "progressive muscular atrophy." The arm has gradually wasted since then and lately has been sore. Otherwise the patient is apparently in good health.

The Wassermann reaction was negative.

DISCUSSION

DR. FRANCES TORREY: The lesions are very sensitive to pain.

DR. N. N. EPSTEIN: One lesion on the back of the neck seems to me to be fluctuant. If this is true, laboratory studies should be made to rule out fungous disease. I think that the diagnosis can be made only by histologic study and culture.

DR. J. M. GRAVES: I think that the condition probably is leprosy.

DR. HIRAM E. MILLER: I think it is suggestive of lymphoblastoma.

DR. A. E. INGELS: The nerves are greatly thickened on both sides.

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: The left ulnar nerve seems to me decidedly atrophic and soft, and the right is thickened and hardened.

DR. G. V. KULCHAR: I do not think that the nerves are thickened. The condition looks to me more like a tuberculoid type of leprosy, although it may be lymphoblastoma.

DR. MERLIN TREVOR-ROPER MAYNARD, San Jose, Calif.: Leprosy is, I think, the diagnosis most strongly suggested.

LOS ANGELES DERMATOLOGICAL SOCIETY

KENDAL FROST, M.D., *Chairman*

CHARLES R. CASKEY, M.D., *Secretary*

May 9, 1939

Parapsoriasis (en plaque type)? Presented by DR. NELSON PAUL ANDERSON and DR. O. M. STOUT (by invitation).

N. P., a white man aged 48, presents an eruption which began in 1932 as small brown macules on the medial aspects of both thighs. They gradually increased in size and number until the upper parts of both thighs became involved. More recently the medial and posterior aspects of both arms have shown similar lesions. The lesions are light brown slightly erythematous scaling macules which coalesce into large plaques.

The blood count was normal, and urinalysis gave negative results. The Wassermann reactions of the blood and the spinal fluid were positive. The patient has been under treatment for meningovascular syphilis since 1933. Local treatment has consisted of the application of Mook's lotion, salicylic acid and sulfur ammoniated mercury and crude coal tar.

DISCUSSION

DR. SAMUEL AYERS JR.: I think the lesions are compatible with the diagnosis of parapsoriasis en plaques.

DR. WILLIAM H. GOECKERMAN: I agree with the diagnosis.

DR. NELSON PAUL ANDERSON: I thought it would be interesting to present this patient for the reason that six years ago a biopsy was performed on one of the lesions. A histologic diagnosis was made of parapsoriasis with possible premycotic changes. A recent report from the laboratory was that if the condition clinically is parapsoriasis, histologically it must be a premycosis fungoides because of the presence of considerably more cellular infiltration than is found in the usual case of parapsoriasis. I think that eventually a frank mycosis fungoides will develop. I think this case raises the question whether there is such an entity as parapsoriasis of the en plaque type, particularly in view of the recent work of H. Keil (ARCH. DERMAT. & SYPH. **38**:545 [Oct.] 1938).

A Case for Diagnosis (Papulonecrotic Tuberculid?). Presented by DR. H. C. L. LINDSAY.

M. G., a white woman aged 62 weighs 223 pounds (101.1 Kg.). Her arms show many areas about the size of the end of a cigaret which present atrophy and telangiectasia. Laboratory tests revealed nothing abnormal except for the presence of sugar in the urine, and this was not found at every test. The local form of treatment has been calamine lotion.

DISCUSSION

DR. SAUL ROBINSON: I was thinking of the possibility of neurotic excoriations. She mentioned insect bites which were present from time to time. I noticed that one of the areas was excoriated.

DR. C. R. HALLORAN: Though the pigmentation in the scars suggests a papulonecrotic tuberculid, the lesions are distributed over areas easily reached by the patient. I favor the diagnosis of neurotic excoriations.

DR. SAMUEL AYRES JR.: I think that the condition is a little vague. The lesions on the arms appear to be some toxic reaction, such as lichen urticatus. Pruritus is

undoubtedly present. I do not think that the itching would be compatible with necrotic tuberculid. Tuberculids also would be more apt to occur on the fingers, legs and ears, as well as on the arms. Then there is the peculiar telangiectasis on the breast and legs and a slight suggestion of it on the back. That also may be some toxic manifestation. I do not know whether the two conditions can be tied together. I have seen widespread spontaneous telangiectasis associated with chronic sinusitis which seemed to be cleared up on treatment of the latter.

DR. IRVING BANCROFT: This woman has diabetes, and that is sufficient cause for a toxic condition. She can scratch and thus produce the scars.

DR. H. C. L. LINDSAY: I believe that the case is one of diabetes in which the patient has itching and produces the lesions by plucking out pieces of flesh. The peculiar telangiectases on the ankles and on the breasts are not artefacts. The lesions that have healed have telangiectases also.

Bowen's Disease (of the Penis). Presented by DR. KENDAL FROST and DR. O. M. STOUT (by invitation).

W. M., a white man aged 58, was circumcised at the age of 21, and there occurred an infection and subsequent scar formation. Four years ago a small vesicle formed at the edge of the scar, and soon thereafter the area became moist and weeping. The area has never healed, in spite of various types of local treatment. There has been a gradual increase in the size of the area for the past two years. At the present time there is on the ventral surface of the penis a crusted indurated area the size of a quarter. The central portion of the area is thicker. The periphery is surrounded with small vesicles.

The Wassermann reaction of the blood was negative. The pathologic diagnosis was epidermoid carcinoma.

DISCUSSION

DR. NELSON PAUL ANDERSON: I think that the condition is one which if it could have been seen one or two years ago would have been diagnosed as erythroplasia. The histologic section reveals an epidermoid carcinoma. The section presents some of the features of a basal cell epithelioma, but this disease does not occur on the glans penis, and probably Bowen's disease does not either. I think the lesion should be treated radically.

DR. H. C. L. LINDSAY: Does not Paget's disease occur on the penis?

Fixed Arsenical Pigmentation. Presented by DR. NELSON PAUL ANDERSON and DR. O. M. STOUT (by invitation).

For J. D., a white man aged 57, a diagnosis of latent syphilis was made in 1935. His first treatments were weekly injections of mercury. On Sept. 4, 1936, weekly injections of 0.2 Gm. of bismarsen were begun. After the nineteenth injection a mild generalized arsenical dermatitis developed, which subsided when the administration of the drug was discontinued, but there remained several reddish brown pigmented macular areas on the thighs and the lower part of the back. These areas have remained about the same.

The Wassermann reaction of the blood was 4 plus.

DISCUSSION

DR. WILLIAM H. GOECKERMAN: On clinical examination I agree that the condition is a drug eruption, but whether it is due to the arsphenamine I am not prepared to say. I can only say that I have not seen a clinical picture like this in cases of fixed arsenical dermatitis. Since the patient has been given bismarsen, is it possible, in the light of some of the cases of fixed pigmentation presented in the past, that this peculiar picture may be due to both bismuth and arsenic? The patient gives a history of unusual sensitiveness to sunlight. I should accept a diagnosis of fixed drug eruption, but further studies are desirable. I suggest patch tests on the pigmented areas.

DR. C. R. HALLORAN: In the group of cases of pigmented eruptions following treatment with arsenicals and bismuth that Dr. Bancroft and I recently reported (*California & West. Med.*, to be published), we encountered none with this peculiar iodine color. However, there were no cases in the group that we studied in which the eruption followed injections of bismarsen. It may be that this particular drug is in some way associated with the peculiar color.

DR. IRVING BANCROFT: I have never seen a condition like the one presented in any fixed pigmentation. It seems to me there should be some examinations to see if there is any abnormality of the fat metabolism.

DR. A. F. HALL JR.: I thought that in view of the peculiar color of the lesions and the fact that the patient was receiving bismarsen when the lesions appeared it would be interesting to give him at intervals injections of neoarsphenamine, a bismuth compound and sulfarsphenamine, to try to determine whether the arsenic, bismuth or sulfur radicals in the bismarsen might be responsible for the peculiar color.

DR. C. R. HALLORAN: I do not believe that a therapeutic test would be of great value. We found that new lesions developed in many patients with continuation of the treatment and that new lesions continued to develop in many patients for some time after treatment had been discontinued.

DR. O. M. STOUT (by invitation): The patient has received bismarsen since the onset of the eruption, and it does not affect the lesions. He gives no history of drugs taken by mouth. He is a total abstainer from alcohol.

A Case for Diagnosis (Ainhum? Syphilis? Periarteritis?). Presented by DR. S. O. CHAMBERS and DR. A. J. GRECO (by invitation).

M. A. C., a Negro aged 49, in 1921 had a penile chancre. Subsequently there was a positive Wassermann reaction. After eight months of antisyphilitic treatment the reaction of his blood was negative, and there was no further treatment until March 20, 1932. He was hospitalized from March 20, 1936 to August 15 for treatment of ulcers of the feet. About 1932 he first noticed thick calluses on the soles and toes. They were soaked and pared off, leaving raw ulcers. Gradually the left great toe sloughed off, leaving a ragged stump. Then the tip of the second toe sloughed off. During 1936 the right great toe became smaller and shorter. On Jan. 6, 1937, at a staff conference of the Veterans Administration Facility at West Los Angeles the following diagnoses were made: (1) tabes dorsalis, (2) chronic alcoholism, (3) atrophy of the optic nerve, (4) neurogenic ulcer of the great toe, (5) syphilitic osteoporosis and (6) arthritis of the toes.

The dermatologic condition is associated with the arthritic deformity of the toes. The left great toe, which has been spontaneously amputated at its metatarsophalangeal joint, has left a ragged stump which is covered with thick callous tissue. The second toes have been partially amputated at their distal joints, the left having lost its nail, and the right great toe is shortened. All the other toes are curled on their metatarsal heads, and all show loss of motion and ulcerated callosities on their dorsal surfaces. Arterial pulsations are normal, and the feet and toes are all of normal color and warmth.

In November 1936 tissue was removed from the ulcer of the right great toe, and a histologic diagnosis of obliterative endarteritis suggestive of syphilis was made. From June to November, 1936 the patient received twenty-three intramuscular injections of a bismuth compound, with indifferent results.

Calluses have been softened with salicylic acid plasters applied three times weekly. The treatment has improved the local condition to some extent, so that the patient can now walk fairly well.

Recently injections of a bismuth compound have been resumed.

DISCUSSION

DR. WILLIAM H. GOECKERMAN: There are a number of possibilities, some probably outside the field of dermatology. I think that there is a trophic dis-

turbance, in which the nervous system is of course involved. I thought at first that the condition possibly might be leprosy, but further examination did not yield corroborative evidence. It is striking that leprosy is as capable of producing variegated clinical pictures as syphilis and tuberculosis and that it need not present a textbook picture. A section of nerve tissue for microscopic study is desirable. I do not believe that the condition is ainhum.

I think that a careful neurologic examination should be made, since the patient complains of numbness of the soles and is seemingly insensitive to pin tests. I could not see much evidence for a vasomotor disturbance, such as Raynaud's disease, not even one that may have run its active course.

DR. NELSON PAUL ANDERSON: It is my impression that when ainhum causes amputation of the toes it usually involves the little toe and that if multiple toes are involved the fourth toe is the one next affected. I agree with Dr. Goeckerman that the patient should be examined carefully with a view to the possibility of leprosy. I received the impression that he had a large ulnar nerve on the left side, although the one on the right was not so prominent. I think it would be well to perform a biopsy of nerve tissue. Syringomyelia can produce this picture, and I should consider syringomyelia or leprosy rather than syphilis.

DR. SAMUEL AYRES JR.: It was not clear to me whether amputation of the toes occurred because of the development of the constriction ring or whether the terminal phalanges became gangrenous and fell off. If there is not any history of a characteristic constriction ring I should be inclined to regard the condition as an endarteritis, possibly of syphilitic origin. I gathered that there was no clinical or spinal fluid evidence of tabes.

PHILADELPHIA DERMATOLOGICAL SOCIETY

JOSEPH V. KLAUDER, M.D., *Chairman*

HERMAN BEERMAN, M.D., *Secretary*

Sept. 15, 1939

Universal Depigmentation of the Skin, with Areas of Hyperpigmentation. Presented by DR. HOWARD EARL TWINING.

J. T., a Negro aged 50, in 1917 first noticed on his chin and hands white spots which gradually became universal. In the summer of 1938 the exposed areas of the skin became blistered after exposure to the sun, after which they became hyperpigmented. The entire cutaneous surface is now white except for the areas of hyperpigmentation on the face, hands and arms.

DISCUSSION

DR. JOHN H. STOKES: I think this patient is interesting because he demonstrates, if his statement about his original color is correct, that there is really hyperpigmentation associated with depigmentation of the skin. Not infrequently it is said that hyperpigmentation is an optical illusion based on contrast between the depigmented skin and the normally pigmented skin, possibly accentuated by exposure to sunlight. But this man has extremely dark spots which clearly illustrate the marked hyperpigmentation phase of the leukodermic picture.

DR. JACQUES P. GUEQUIERRE: The patient also stated that he worked in a steel mill and that some of the areas of hyperpigmentation are where pieces of steel and slag struck his skin.

A Case for Diagnosis. (Erythema Multiforme? Pemphigus? Dermatitis Herpetiformis?). Presented by DR. ABRAM STRAUSS.

B. B., a white boy aged 16, presents a more or less generalized wheal-like eruption, with some of the lesions surmounted by blebs and others by pustules.

There is considerable itching, and at times the patient has had mild fever. He was first seen on April 4, 1939, with a severe dermatophytosis of the hands, associated with pyoderma and considerable edema. There was slight fever and axillary lymphangitis. This condition cleared up except for some lesions around the finger nails. The present condition began four weeks ago with blebs under the upper part of the right arm and then gradually spread. Fungi were found by culture and microscopic examination during the first attack, but none have been found in the present one. A blood count showed 75 per cent hemoglobin, 3,800,000 erythrocytes per cubic millimeter and 11,800 leukocytes per cubic millimeter. Soothing lotions and sulfanilamide have been administered, with apparent control of the lesions.

DISCUSSION

DR. ERICH URBACH (by invitation): It seems to me that this condition is a bacterid.

DR. JOHN H. STOKES: I think the condition is the erythema multiforme or pemphigoid or pemphigus-like type of bacterid, which has been described by Bruusgaard (*Brit. J. Dermat.* **34**:150 [May] 1922). He reported a case in which a typical erythema nodosum was traced directly to a fungous infection, kerion celsi of the skin. In fact, fungi were recovered, I believe, from the patient's blood. I cannot see why it is so difficult to imagine a secondary dermatitis, such as so commonly occurs after sensitization by fungi. The second phase may be more pustular than the first. What interested me most was the statement that "cauliflower" ears developed about four days after the sulfanilamide therapy was stopped. Dr. Flood and I have been impressed with that peculiarity of the effect of sulfanilamide. The drug appears to be, for dermatologic lesions, bacteriostatic rather than bactericidal. The cessation of the administration of the drug may be followed by a relapse of the original eruption. I have a feeling that some conditions diagnosed as toxic eruptions due to sulfanilamide are really violent flares on the order of a syphilitic relapse. In a case in which there is diminished resistance and no developed defense, a relapse may perhaps occur and not a toxic eruption due to sulfanilamide. In this case the development of the condition of the ears and the erythema-multiforme–like eruptions on the face four days after the stopping of the ingestion of sulfanilamide seems to me deserving of investigation from that standpoint. There may be an interplay between virus infections and fungous infections and between fungous infections and superimposed virus infection. Possibly some of the conversion forms of streptococci, which become so small that they are filter passing, are the bacterid agents. One may fail to find a certain organism, and cultures may frequently fail to give positive results, because the organism has passed into this different form. I think that here is a field for investigation which may yield observations of importance in the future.

DR. ABRAM STRAUSS: Will further administration of sulfanilamide aggravate or help the patient under discussion?

DR. JOHN H. STOKES: I think it would be well to try it again. The action of the drug may be controlled by watching the blood count. I do not think the drug should be given to the boy unless he is hospitalized and the effect on the blood is observed by daily counts.

DR. HERMAN BEERMAN: This case reminds me of one that Dr. Fondé and Dr. Goldberg described, in which a patient with lymphogranuloma venereum was treated with an antimony compound (ARCH. DERMAT. & SYPH. **34**:478 [Sept.] 1936).

A Distinctive Type of Tuberculosis in the Negro Associated with Tuberculous Keratouveitis. Presented by DR. ELMER R. GROSS, Wilmington, Del.

H. G., a Negress aged 40, was first seen in March 1935, with uveitis of both eyes. The Wassermann reaction of the blood was strongly positive. The vision was 6/9 in the right eye and 6/15 in the left eye. She was given fifty injections of

a bismuth compound, thirty-six injections of neoarsphenamine and oral doses of potassium iodide between March 1935 and November 1937. In August 1936 the Wassermann reaction of the blood was negative, and tests of the spinal fluid gave negative results. In November 1936 a cutaneous lesion appeared on the right thigh and was followed by the gradual development of lesions elsewhere.

Examination of both extensor surfaces of the legs reveals discoid elevated and infiltrated plaques about 2 cm. in diameter, some of which are smooth, others atrophic and depressed and others scaly. There are also some plaques on the back and a few on the lower side of the chest following the lines of cleavage. There are a few split pea–sized lesions on the face and the atrophic remains of lesions on the scalp. The patient is well developed but poorly nourished. Roentgenograms showed evidence of pulmonary tuberculosis but no changes in the bones of the hands. Examination with a slit lamp revealed hazy corneas and numerous large and small mutton fat grayish deposits on their posterior surfaces. The von Pirquet reaction in November 1937 with a dilution of 1 : 10,000 was negative. The reaction in June 1939 with dilutions of 1 : 10,000 and 1 : 1,000 was negative. On April 17, 1939 the vision in the left eye was 6/60 and in the right eye was limited to light perception. Histologic examination of a cutaneous lesion revealed typical tuberculous architecture.

DISCUSSION

DR. EDWARD F. CORSON: Dr. Ludy had a patient with a similar type of cutaneous eruption and with one eye blind and vision in the other was limited to light perception. This form of tuberculosis is commonly observed in the Negro. Often a depigmented ring surrounds a granulomatous lesion. One sees the same rounded patches as this woman shows on the cheeks. The condition is not lupus vulgaris, tuberculosis verrucosa cutis or scrofuloderma, and I should appreciate knowing in what category to include it.

DR. JOSEPH V. KLAUDER: Dr. Weidman and I have regarded this as a distinct type of tuberculosis in the Negro. Others think that it is another expression of Schaumann's disease. If the latter conception is the correct one, I think the condition should be regarded as an unusual expression of Schaumann's disease.

Lupus Erythematosus. Presented by DR. ELMER R. GROSS, Wilmington, Del.

E. S., a white man aged 29, was presented at a previous meeting (Jan. 21, 1938) with the diagnosis of lupus erythematosus or sarcoid. He is now presented with the diagnosis of lupus erythematosus, the histologic report and clinical improvement being consistent with this diagnosis. He now presents a disappearing remnant of a lesion on the right supraorbital ridge and a dime-sized lesion on the left supraorbital ridge. The patient was treated with two courses of a bismuth preparation, a saltless diet and hygienic measures.

Nickel Dermatitis (from Spectacle Frames). Presented by DR. ELMER R. GROSS, Wilmington, Del.

M. P., a white woman aged 43, appearing to be in good general health, presents a subacute dermatitis of both supraorbital regions and along the line of the temples and the ear pieces of the glasses. The upper part of the chest is the site of a similar eruption. The result of a patch test made with scrapings from her spectacle frames was positive.

DISCUSSION

DR. JOHN H. STOKES: I think some persons hesitated to accept the sensitization conception of this condition because of the eruption on the chest. I have noticed the possibility of the association of nickel with pyogenic infection. The pyogenic infection may lead to nickel sensitization, and the nickel sensitization can certainly lead to an overwhelming spread of the original pyogenic infection, extending far

beyond the area in contact with the nickel. I have seen the contact of a nickel truss in the groin result in an extensive flare. Spectacles can cause the same result. The process will extend down the nose and out on the face, and then isolated pustules, extensions of the process, may be scattered over the shoulders. That, I should say, is the probable explanation of the eruption on this woman's chest.

DR. THOMAS BUTTERWORTH, Reading: Another explanation for the eruption on the chests of these patients was illustrated by a patient I saw recently. She had nickel dermatitis on her head where the skin came in contact with her glasses and on her chest where the skin came in contact with the little nickel-plated piece of metal used in adjusting the length of the straps of her slip. There was an area of dermatitis possibly 2 to 3 inches (5 to 7.5 cm.) in diameter on the upper part of the pectoral region of each side. The same patient showed dermatitis over the region in contact with the white gold band of her wrist watch and two palm-sized areas of inflammation on the front and back of the thighs where the nickel of the garters came in contact with the skin. It might be wise to check as to whether nickel of an adjustable band on this patient's slip is the source of the eruption on her chest.

Primary Atrophy of the Optic Nerve; Juvenile Tabes Dorsalis. Presented by DR. MARJORY HARDY, Norristown, Pa. (by invitation).

L. C., a Negress aged 19, was first seen in June 1939, when she said her vision had been getting worse for the past two months. Her vision on June 1, 1939, was 6/12 in the right eye, and all she could see with the left eye was movements of the hand. On June 17, 1939, it was 6/15 plus 2 in the right eye, and the left eye was blind. Her facies is normal, and her joints and tibias are normal. She has an open bite. The teeth are dwarfed, with some appearing deciduous. The upper central incisors are dwarfed but are not of the hutchinsonian type. On the left side there are mulberry molars in both the upper and the lower jaw. The pupils are irregular and do not react to light. The patellar reflexes are absent, and the Romberg sign is positive. The Wassermann reaction of the blood was positive. The examination of the cerebrospinal fluid showed 133 lymphocytes per cubic millimeter; reaction for globulin, weakly positive; Meinicke reaction, strongly positive; Wassermann reaction, strongly positive, and colloidal gold curve, 1233100000. The patient was inoculated with malaria organisms, but no rise in temperature or chills followed. She has received neoarsphenamine and injections of a bismuth preparation.

DISCUSSION

DR. JOHN H. STOKES: I wish to comment on the extraordinary behavior of juvenile tabes in some cases. This point was demonstrated to me by a patient whom I first saw nearly twenty years ago. His father had neurosyphilis; his mother had latent syphilis; his brother had all the stigmas of congenital syphilis, and this boy had tabes with gastric crises which frequently taxed all my resources to the limit to pull him through alive. Now he is grown and married and has a child. The sole residue of his gastric crises is what I think is a fear neurosis, which causes him to be nauseated every morning at an appointed hour and for an appointed time, after which he is able to rise and go about his business. No fewer than eight Charcot joints have developed; his feet have spread into flippers; he has more Charcot toes than normal toes, not counting the amputations; at least seven vertebrae have been almost completely absorbed by Charcot changes in his spine; his deep reflexes are still present; he still has libido and potentia, but he has lost the stereognostic sense in his hands, so that he cannot distinguish nickels from quarters and consequently cannot make change. Apart from these disturbances, he is a living member of society. His health was nearly ruined recently by his driving to the San Francisco Fair from the city in South Dakota in which he lives. He drove 7,000 miles over roads of unparalleled roughness, because he wanted to see the mountains. Dr. George Wilson, the neurologist, said that this experience left him nervously collapsed; but his peripheral nervous changes, numbness and paresthesias are not

ascribable to irritation of the dorsal roots or to any effect from his Charcot spine whatever. He thinks these processes are peripheral and that the patient can be materially improved by large doses of vitamin B_1. The man is now about 32 years of age, and apart from some stormy episodes has managed to weather juvenile tabes that started in the second year of his life.

DR. JOSEPH V. KLAUDER: The fact that the patient presented is a Negro is of interest. I cannot recall having seen juvenile tabes in a Negro. One may question whether the infection is congenital. The age would suggest this origin, but perhaps less so in the Negro race. I think the open bite she presents is definite evidence of congenital syphilis. It is the only structural abnormality she has which is characteristic of the so-called stigmas of congenital syphilis. I think the open bite is perhaps the second most significant dental abnormality found in congenital syphilis. It is not so significant as Hutchinson's teeth, but is more significant than mulberry molars. The prognosis of the atrophy of her optic nerve is not necessarily bad, since malaria therapy may save the vision in her good eye. Since she is a Negress, it is questionable whether she can be inoculated with malaria successfully. If she cannot, she should receive mechanical fever therapy.

Darier's Disease, with Possible Nevoid Changes on the Forehead.
Presented by DR. HAROLD M. JOHNSON (by invitation).

M. G., a white man aged 43, well developed, dusky in appearance but apparently in good health, presents a leonine expression because of the infiltration and induration of the supraciliary folds and frontal area of the head. There is a vegetative fungoid lesion 4 cm. in diameter on the right side of the forehead. Several pedunculated lesions 2 by 3 cm. in diameter are scattered over the scalp. Both retroauricular folds have hyperplastic vegetative lesions that almost completely obliterate the spaces. The face is indurated with hyperkeratotic nodules, giving the leonine expression. On the back are confluent keratotic papules. There are many keratotic lesions scattered over the scapular and infrascapular areas, and they are somewhat greasy to touch. These lesions become less numerous toward the sacral region. There are similar hyperkeratotic papules and plaques on the sternal and inframammary regions. The groin presents coalescence of the papules and a purulent exudate. In the intergluteal fold is a large cauliflower-like lesion. The legs, palms and soles are relatively uninvolved. The dorsa of the hands are roughened and keratotic. Seventeen years ago the patient had a "boil on the rectum," which developed into a large ulcer and opened and drained for several years. In 1932 he noticed small vesicles and papules on the lower part of the sacral region. These gradually increased in size and number and spread up the back. The lesions were intensely pruritic and were worse in summer. Several years later his thorax became involved. Five years ago he noticed two small pustules on the side of his nose, which he frequently squeezed with his fingers. Later, pruritic pustules appeared on the forehead and the cheeks. The forehead has become involved only during the past two years. The retroauricular areas have become thickened and hyperplastic during the last year. In spite of treatment the disease has progressed.

DISCUSSION

DR. JOHN H. STOKES: I have done some thinking about this case, without arriving at any satisfactory conclusion. I happened coincidentally to see what might be thought of as the beginning of such a process in a young man with verruciform epidermal dysplasia. I wonder whether this man might have some type of dysplasia which might be completely blanketed by the Darier's disease. I shall have to accept it as Darier's disease on the basis of the histologic observations and say that there is something uncomfortably nevus-like about the appearance of the facial lesions and that he may have an epidermal dysplasia of some sort or even some type of fat gland nevus.

DR. THOMAS BUTTERWORTH, Reading: This is a typical example of Darier's disease, showing the pronounced scaly papular lesions of the scalp without loss of

hair, the keratosis of the backs of the hands, the diffuse yellowish keratotic thickening of the palms and soles and the fungating lesions in the groins and between the buttocks. A brother has a similar condition, and a sister did not have the disease. The patient cannot give any history of his parents, because his mother died while he was young and he has seen his father only once in his life. Involvement of 66 per cent of the sibship is in accordance with the dominant inheritance characteristic of Darier's disease, in which the theoretic incidence would be 50 per cent.

Late Secondary Syphilis with Pyogenic Infection and Syphilitic Dactylitis. Presented by DR. MARJORY HARDY, Norristown, Pa. (by invitation).

A. M., a white woman aged 28, presents an ulcerated lesion 1 cm. in diameter, covered with a grayish membrane, on the right side of the soft palate. There are many heavily crusted lesions on the arms, legs, trunk and face. These vary in size from 0.5 to 5 cm. Some of them are dry, some are surrounded by an area of redness, and some are indurated and have a punched-out appearance. There is a hard papule on the right ankle. On Aug. 29, 1939 the patient had a sore throat, headache and chill; three weeks previously a generalized eruption had developed, and about August 15 the right eye had become inflamed. The patient's temperature was slightly elevated. Just prior to the patient's admission a window fell on the fourth finger of her left hand. A roentgenogram showed a fracture, advanced osteomyelitis involving the distal phalanx and a considerable amount of bone destruction. The Wassermann reaction of the blood was strongly positive. She has had only one injection each of a bismuth compound and of neoarsphenamine.

DISCUSSION

DR. DONALD M. PILLSBURY: On morphologic grounds, it is much more likely that this condition is either iododerma or bromoderma. The patient stated that she takes bromo seltzer once a week and took some just previous to the onset of this condition. The lesions are highly inflammatory, and those over the legs are granulating and show a tendency to ulcerate; some of the lesions on the face are button-like and pustular. More proof is needed to decide whether the condition is late secondary syphilis.

DR. JOSEPH V. KLAUDER: The lesions are not by any means typical of an eruption due to secondary syphilis. I think that diagnosis was based on the fact that syphilis is apparently definitely established by the appearance of the throat and by the results of serologic tests. Some of the lesions are definitely infiltrated. There is one on the sole which is certainly suggestive of syphilis. The smooth surface does not suggest a bromoderma, but the ulcerating lesions on the legs, I think, do. There are some lesions with central ulceration and others with a pyogenic crust.

Trichomycosis Axillaris Flava Associated with Alopecia Prematura, Alopecia Areata (Chin) and Fragilitas Crinium (Eyebrows and Upper Lip). Presented by DR. REUBEN FRIEDMAN.

H. N., a white man aged 21, presents on the scalp an abundance of thick black hairs, many of which, however, are easily loosened and extracted on running one's hand through them with gentle traction. The removed hairs reveal no gross abnormalities. The eyebrows are thinned, and some of the hairs are broken; none have nodes. The skin of the axillas presents a thinning of the hair, and many of the hairs present irregular firm yellowish nodular masses along and either partly or entirely surrounding the shafts. There is also splitting of the free ends of some of the axillary hairs. There is no similar involvement of the pubic hairs, although some of them are extracted with ease. The hair on the chest is thinned. The serologic reactions of the blood were negative. This patient is presented on account of the unusual association of four different types of hair lesions (in other words, multiple trichopathies), which according to reports in literature is not uncommon. Lane (*J. Cutan. Dis.* **39**:387, 1919) reported having found 51 instances in an examina-

tion of 128 men drafted for the army. That would make an average of 2 in every 5 adult males. It seems to me, however, that this is a proportion far greater than is ordinarily encountered.

DR. ERICH URBACH (by invitation): I should not say that 2 of every 5 males abroad have this condition, but I should say that one could see it nearly every day if one were interested in looking for it. It occurs especially in tuberculous persons.

Pityriasis Rosea in an Infant. Presented by DR. JOSEPH V. KLAUDER.

C. G., a Negro child aged 6 months, presents scaly lesions varying in size from 1 to 2 cm. distributed over the upper part of the back, the sides of the nose and the right side of the face. The condition began three weeks ago on the right side of the face and then appeared on the back and neck. There are no subjective symptoms.

DISCUSSION

DR. DONALD M. PILLSBURY: This pityriasis-rosea-like eruption is commonly encountered, but more frequently in Negro children. I see many examples at the Children's Hospital. I diagnose the eruption as a superficial type of ringworm infection but have never been able to prove the fungous origin. I believe the eruption is related to achromia parasitica, and this child has some depigmentation round the hairline. I think this condition is a common dermatosis. I do not know exactly what it is but I feel certain that it is not pityriasis rosea.

DR. JACQUES P. GUEQUIERRE: I did not think the patient had pityriasis rosea. I have never found fungi in this condition.

DR. JOSEPH V. KLAUDER: It is unusual to see pityriasis rosea in an infant. The condition to which Dr. Pillsbury refers is not likely to present so many lesions as does the eruption in this patient. Moreover, in that condition the lesions do not follow the lines of cleavage of the skin as they do in this patient. It is this feature that suggests pityriasis rosea.

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